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STRUCTURE OF THE FILUM TERMINALE

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BROOKLYN

The histologic structure of the filum terminale is of neuroanatomic interest and clinical importance; yet the descriptions in the medical literature are fragmentary and inadequate. Modern metallic methods have been utilized in this study to demonstrate the cytologic structure of the filum and its transition to the conus medullaris.

The filum terminale was at one time called the "nervus impar," Haller later expressing the view that it was formed by attachment of the vascular covering of the spinal cord to the coccyx (Rauber [1]). That the filum contains nerve tissue was soon appreciated by many investigators. Clark [2] described the filum terminale as a cylindric tubule which becomes enlarged at the conus medullaris. This dilatation of the ependymal canal was called the ventriculus terminalis or the fifth ventricle by Krause.[3] Saint-Remy [4] was unable to find a dilatation of the ependymal canal in adults comparable to that which Krause and, later, Tourneux [5] and Bräutigam [6] described. Saint-Remy expressed the belief that the disappearance of the canal in adults indicated its fetal nature and that it did not, therefore, merit the name "ventricle"—he called it the "sinus terminale." Argutinsky,[7] on the other hand, con-

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1. Rauber, A.: Die letzten spinalen Nerven und Ganglien, Morphol. Jahrb. **3**:603, 1877.

2. Clark, J.: Further Researches on the Grey Substance of the Spinal Cord, Phil. Tr., London **149**:437, 1859.

3. Krause, W.: Der Ventriculus terminalis des Rückenmarks, Arch. f. mikr. Anat. **11**:216, 1875.

4. Saint-Remy, G.: Recherches sur la portion terminale du canal de l'épendyme chez les vertébrés, Thesis, Nancy, no. 246, 1887.

5. Tourneux, F.: Sur la structure et sur le développement du fil terminal de la moelle chez l'homme, Compt. rend. Soc. de biol. **4**:340, 1892.

6. Bräutigam, H.: Vergleichend-anatomische Untersuchungen über den Conus medullaris, Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. a. d. Wien. Univ., 1892, p. 111.

7. Argutinsky, P.: Ueber die Gestalt und die Entstehungsweise des Ventriculus terminalis und über das Filum terminale des Rückenmarkes bei Neugeborenen, Arch. f. mikr. Anat. **52**:501, 1898.

sidered the ventriculus terminalis a true ventricle, developing as the result of growth of cells in the walls of the primitive cavity. Kernohan [8] concluded from a study of the growth curve of the ventriculus terminalis in a group of fetuses, newborn infants, children and adults that it was a true ventricle and not merely a sinus or an embryonic rudiment. Harmeier [9] confirmed previous observations that the interstitial cells of the intradural portion of the human filum are the same as those seen in the spinal cord. Microglia cells, however, were not observed (Kernohan, Woltman and Adson [10]). These cells were later demonstrated in the intradural portion of the filum by Tarlov.[11] Neuroblasts were said to occur in the intradural portion by Harmeier and by Kernohan, Woltman and Adson.

Kunitomo [12] showed that in very young human embryos the spinal cord reaches the extreme tip of the tail and throughout its length is uniform in structure. Somewhat later it can be divided at about the level of the thirty-second vertebra into a cranial part, having a wide central canal and thick walls, and a caudal part, having a narrow canal and thin walls. He showed that it is the caudal portion that undergoes regressive changes, forming the filum terminale. Kunitomo, like Braun,[13] pointed out that there are two factors involved in the formation of the filum terminale: (1) elongation due to the relatively more rapid growth of the vertebral column than of the spinal cord, the latter being attached to the coccyx, and (2) dedifferentiation (reversion of tissue to an earlier embryonic type, with subsequent redifferentiation) of the caudal end of the medullary canal. Streeter [14] evaluated the role of each factor in the formation of the filum by determination of the elongation of the nerve roots. He concluded that the filum terminale "like the sacral nerve roots, elongates by interstitial growth in adaptation to the ascending displacement of the spinal cord, rather than as a result of a simple stretching."

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8. Kernohan, J.: The Ventriculus Terminalis: Its Growth and Development, J. Comp. Neurol. **38**:107, 1924-1925.

9. Harmeier, J.: The Normal Histology of the Intradural Filum Terminale, Arch. Neurol. & Psychiat. **29**:308 (Feb.) 1933.

10. Kernohan, J.; Woltman, H., and Adson, A.: Gliomas Arising from the Region of the Cauda Equina, Arch. Neurol. & Psychiat. **29**:287 (Feb.) 1933.

11. Tarlov, I.: Ependymoma of the Filum Terminale, Arch. Neurol. & Psychiat. **32**:1045 (Nov.) 1934.

12. Kunitomo, K.: The Development and Reduction of the Tail and of the Caudal End of the Spinal Cord, Contrib. Embryol. **8**:161, 1918.

13. Braun, M.: Entwicklingsvorgänge am Schwanzende bei Säugethieren mit Berücksichtigung der Verhältnisse beim Menschen, Arch. f. Anat. u. Entwcklngsgesch., 1882, p. 207.

14. Streeter, G.: Factors Involved in the Formation of the Filum Terminale. Am. J. Anat. **25**:1, 1919.

MATERIAL AND METHODS

Human material was used exclusively in this study, fila being taken from about 25 subjects, of various ages and both sexes. For measurements of the conus medullaris and the filum terminale, dissections of the lower end of the vertebral canal were made and measurements taken with the spinal cord intact. In this way the boundaries between the conus and the filum could be accurately determined with the nerve roots and ganglia clearly exposed. The methods used in this study were those referred to in a previous article.[15] Some of the material was studied in serial sections.

OBSERVATIONS

A. Gross Relationships.—The filum terminale is the slender, glistening prolongation of the end of the conus medullaris. The fourth sacral segment marks the beginning of the conus medullaris, as suggested by Van Gehuchten and de Neeff[16] on the basis of their observation that the cells innervating the muscles of the lower limb disappear at this level. It is further convenient to accept the filum terminale as beginning beyond the point of origin of the last spinal nerve roots. The conus medullaris then includes the last two sacral segments and the first coccygeal segment,[17] the intradural portion of the filum terminale extending from the end of the last coccygeal segment to the point of closure of the dural sac over the filum (i. e., the second sacral vertebra). The extradural portion of the filum terminale continues from the site of dural closure over the filum to the back of the coccyx, to which it is attached.[18] The transition between these structures is gradual, although occasionally a dilatation of the central canal (ventriculus terminalis, fig. 1) marks the boundary. For measuring the length of the conus medullaris it is necessary to identify the fourth sacral roots, which are considerably smaller than the roots above. Hovelacque[19] pointed out that the volume of the sacral roots changes below the second sacral root. The third sacral roots are about one-half as thick as the second,

15. Tarlov, I.: Structure of the Nerve Root: I. Nature of the Junction Between the Central and the Peripheral Nervous System, Arch. Neurol. & Psychiat. **37**:555 (March) 1937.

16. Van Gehuchten, A., and de Neeff, C.: Les noyaux moteurs de la moelle lombosacrée chez l'homme, Névraxe **1**:201, 1900.

17. The roots of the first coccygeal nerve sometimes run within the pial sheath of the intradural portion of the filum. In such cases the beginning of the filum is taken as 6 mm. below the exit of the last sacral nerve root, since the coccygeal roots usually extend approximately this distance along the conus.

18. Luschka (1860, quoted by Rauber) first called attention to the two segments of the filum (the filum terminale internum, or the intradural portion of the filum terminale, and the filum terminale externum, or the extradural portion).

19. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du système grand sympathique, Paris, Gaston Doin & Cie, 1927.

and the fourth and fifth sacral roots are much thinner (fig. 2). In a few instances a small fusiform ganglion was present along the posterior coccygeal root, several centimeters from its origin, the anterior root joining the distal end of the ganglion to form a true spinal nerve. Usually the delicate anterior coccygeal roots arise near the anterior spinal vein, caudal to the posterior roots, which arise from the posterior lateral sulcus.

The measurements of the conus medullaris and the filum terminale vary considerably. In a newborn infant the conus measured 1.2 cm.,

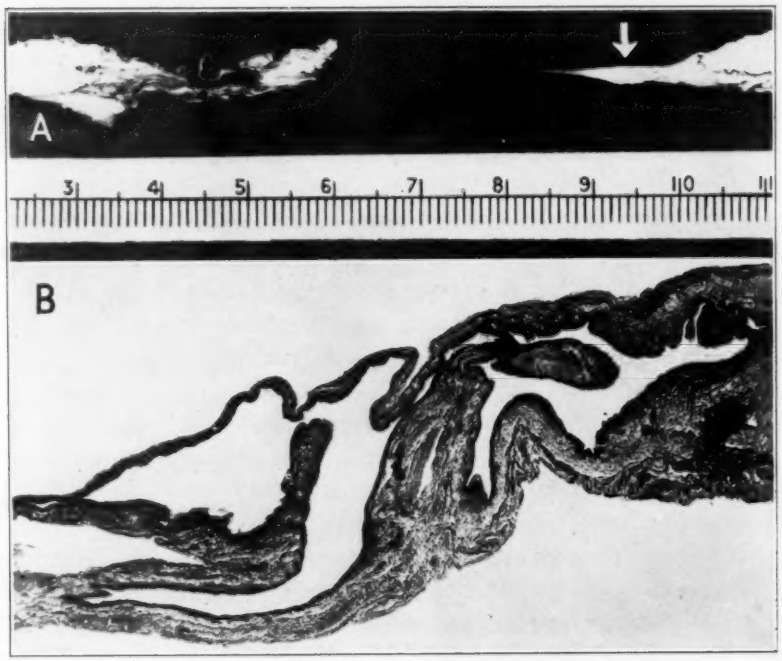

Fig. 1.—*A*, photograph showing the ventriculus terminalis (at the arrow) in a 5 week old infant. *B*, ventriculus terminalis in a 5 week old infant. The conus medullaris is shown on the right, and continuation of the filum terminale, on the left. Hematoxylin and Van Gieson stain; × 18.

the intradural portion of the filum 4.2 cm. and the extradural portion 2.2 cm. The length of the conus and filum is directly proportional to the body length, although minor variations exist among subjects of the same height. For adults the average measurements found were: 1.7 cm. for the conus medullaris, 15 cm. for the intradural portion of the filum terminale and 7.5 cm. for the extradural portion.

The filum terminale is surrounded by a glistening connective tissue sheath continuous with the pia mater at higher levels. The sheath often

presents longitudinal silvery bands of connective tissue. The ligamentum denticulatum, which extends as a narrow band along the lateral aspect of the pia mater, becomes continuous with the sheath of the filum. One sometimes sees strands of nerve fibers running within the sheath, which probably represent the second and third, as well as the first,

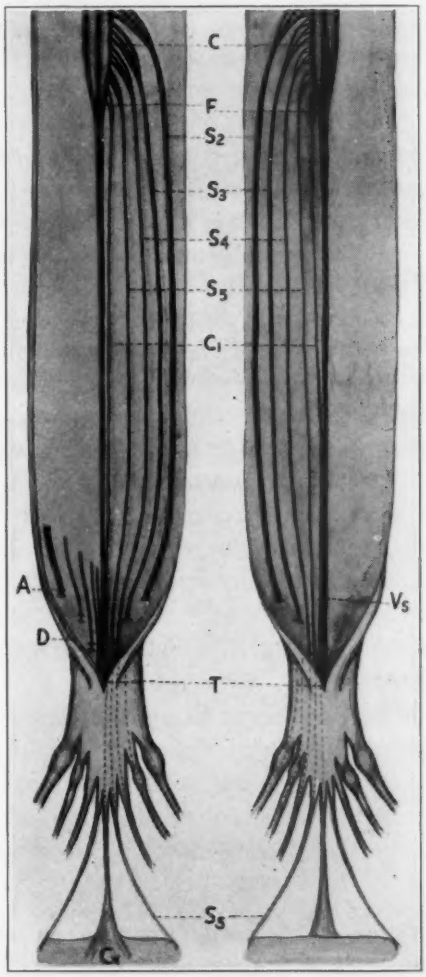

Fig. 2.—Drawing of the filum terminale and lower end of the spinal cord. Dorsal roots are shown on the left, and the ventral view, with the anterior roots, appears on the right. *A* is the arachnoid, shown on the left half of the dorsal view, with nerve roots piercing it just proximal to the dural aperture; *C*, the beginning of the conus medullaris, just below the third sacral nerve root; *Cx*, the fusion of the extradural portion of the filum terminale to the periosteum over the coccyx; *D*, the dura mater; *F*, the beginning of the filum terminale, just below the first coccygeal nerve root; *T*, the transition from the intradural to the extradural portion of the filum terminale, and *Vs*, the anterior spinal vein.

coccygeal nerves, as Rauber (1877)[20] pointed out. The first coccygeal nerve runs along the filum, receiving finally its own arachnoid and dural investments. The fifth sacral nerve, as well as the nerves at higher levels, make their exit through separate arachnoid and dural apertures.

B. Microscopic Structure.—1. Intradural Portion of the Filum Terminale: (*A*) Nerve Cells. The chief respect in which the fourth sacral segment, or the beginning of the conus medullaris, differs from the third sacral segment is in the absence of the large cells of the lateral cell group.[21] This feature was recognized by Müller,[22] Onuf,[23] Van Gehuchten and de Neeff [16] and Bruce.[24] The anterior horns of the fifth sacral segment become reduced, being smaller than the posterior horns, whereas in the fourth sacral segment the two are more nearly equal. Occasional large cells occur in the anterior horns of the fifth sacral segment. In the coccygeal segment the large anterior horn cells are rarely seen, and the number of nerve cells in general is greatly reduced; also at this level the anterior and the posterior horns become similar in appearance, and the distinction between the gray and the white matter is less marked than at levels above. The lack of demarcation between the gray and the white substance is even more pronounced in the filum terminale. Well preserved nerve cells have been encountered along the first 3 cm. of the intradural portion of the filum. These cells are small for the most part and are often elongated or polar. Occasional large multipolar cells, like those of the anterior horn, occur in the filum. Nerve cells sometimes occur along the nerve fiber tracts of the filum, occasionally at their lateral margins, along the connective tissue sheath. While most of the nerve cells of the filum appear normal, degenerating forms are encountered.

(*B*) Nerve Fibers. The nerve fiber tracts of the conus medullaris continue for variable distances within the intradural portion of the filum, becoming less marked caudally and usually disappearing as well defined tracts within its upper half. The nerve fibers of the posterior column become dispersed proximal to the site at which the anterolateral column

20. Rauber cited a case reported by Schlemm (1837) in which thirty-two, instead of thirty-one, pairs of spinal nerves occurred, the second coccygeal nerve presenting an anterior and a ganglionated posterior root.

21. Occasional large cells have been seen in the lateral cell column, but the change in the number of these cells from the third to the fourth sacral segment is striking.

22. Müller, L.: Untersuchungen über die Anatomie und Pathologie der untersten Rückenmarksabschnittes, Deutsche Ztschr. f. Nervenh. **14**:1, 1898.

23. Onuf, B.: Notes on the Arrangement and Function of the Cell Groups in the Sacral Region of the Spinal Cord, J. Nerv. & Ment. Dis. **26**:498, 1899.

24. Bruce, A.: Topographical Atlas of the Spinal Cord, London, Williams & Norgate, 1901.

disappears. At lower levels the nerve fibers become scattered along neuroglia or ependymal cells. Most of the nerve fibers gradually attain the periphery of the filum over a course of from a few millimeters to several centimeters. They course within the connective tissue sheath of the filum as small bundles surrounded by Schwann cells and endoneurium and occasionally containing nerve cells. In view of the small size of these bundles of nerve fibers and the obliquity of their course, the exact site of superficial origin (i. e., the site at which the centrally ensheathing cells of the nerve fibers are replaced by Schwann cells and endoneurial cells) cannot be determined.

Many of the nerve fibers of the filum are myelinated, and some are of fine caliber. Toluidine blue stains, following fixation in Müller's fluid, reveal only occasional purple granules (π or protagon-like granules) around the nuclei of Schwann cells. Since the number of these granules has been observed to parallel closely the number and size of the myelin sheaths, it follows that some of the peripheral nerve fibers of the filum are nonmyelinated or are surrounded by fine myelin sheaths. Furthermore, comparison of sections stained for myelin sheaths with those taken at the same level of the filum in which axis-cylinders are impregnated makes it clear that a considerable number of the nerve fibers are nonmyelinated.

(*C*) Ependyma. Ependymal cells are the most numerous of the interstitial cells of the intradural portion of the filum. They form an extensive mosaic, or rings and canals of varying sizes. The rings surround clear spaces, groups of ependymal cells, blood vessels, balls of connective tissue, amorphous material or débris. Occasionally a droplet of fat may be seen at the center of an ependymal ring. A well defined cuticle formed by the inner processes of the ependymal cells may occur. Not infrequently, however, such a cuticular membrane is absent, the canals presenting invaginations of ependymal cells into their lumens. In some instances various stages of degeneration could be traced between the normal ependyma around the canal and the débris within its center. Ependymal cells are sometimes bordered by nerve fibers which are surrounded by oligodendrocytes and astrocytes. Occasionally one sees ganglion cells surrounded by large groups of ependymal cells through which nerve fibers may course for long distances. Such nerve fibers have never been seen to enter the lumen of the canal. They sometimes loop through ependymal areas from the fiber tracts of the filum, in which region they are covered by oligodendrocytes and astrocytes. It has not been possible to trace nerve fibers from ependymal areas directly to their peripheral segments, to determine the nature of the transition site.

The central canal of the filum is usually greatest in extent near its junction with the conus medullaris. It may reach the dorsal border of the filum. Often the central canal may bifurcate or present several outpouchings, so that on transverse section several canals of different caliber may appear (fig. 3 *A*). The central canal may disappear and then reappear at a lower level. It usually terminates within the first half of the intradural portion of the filum. While most of the ependymal cells are of short cuboid or columnar type, one occasionally sees cells lining the central canal with single tapering peripheral processes, occasionally branched, which may abut blood vessels or connective tissue. Such tailed cells may occur anywhere around the central canal, although they seem to be more common along its dorsal and ventral borders. Ciliated ependyma, in which blepharoplasts are sometimes seen, has been encountered occasionally in adults as well as in younger subjects. Ependymal canals are often underlaid by a feltwork of glia fibers, as pointed out by Anglade.[25]

Ependymal cells are the last of the interstitial cells [26] of the filum to disappear, often extending caudally to within 2 cm. of the transition from the intradural to the extradural portion of the filum. As the parenchyma of the intradural portion decreases caudally, it becomes represented by a band of ependymal cells or a few cells wedged among heavy collagen fibers near the dorsal surface of the filum (fig. 3 *C*). An attempt was made to determine whether the ependyma and neuroglia extend relatively farther caudally in the fila of young persons than in those of adults. The variation in normal extent of these cells in the fila of the two age groups examined was so great, however, that the differences were not impressive.

(*D*) Astrocytes. Astrocytes of the filum are chiefly of the fibrous variety (fig. 4 *A*), protoplasmic, as well as some fibrous, forms occurring in the gray matter. The neuroglia fibers course in all directions, forming a dense supporting mesh for the nerve fibers. The marginal layer of the spinal cord, with its small astrocytes, oligodendrocytes and microglia cells, extends along the most cephalic portion of the filum, becoming progressively thinner caudally. It is variable in extent, and even in appearance, since nerve fibers may sometimes extend well to the bordering pial sheath. Astrocytes are attached to blood vessels, the pia mater or connective tissue septums in the filum, as elsewhere. Numerous neuroglia fibers form a stroma among ependymal cells, although in

25. Anglade, M.: La névroglie dans le cône terminal et le filum terminale de la moelle de l'homme adulte, Bull. et mém. Soc. anat. de Paris **78**:37, 1903.

26. The interstitial cells include all the non-nervous cells except those of the blood vessels and connective tissue stroma.

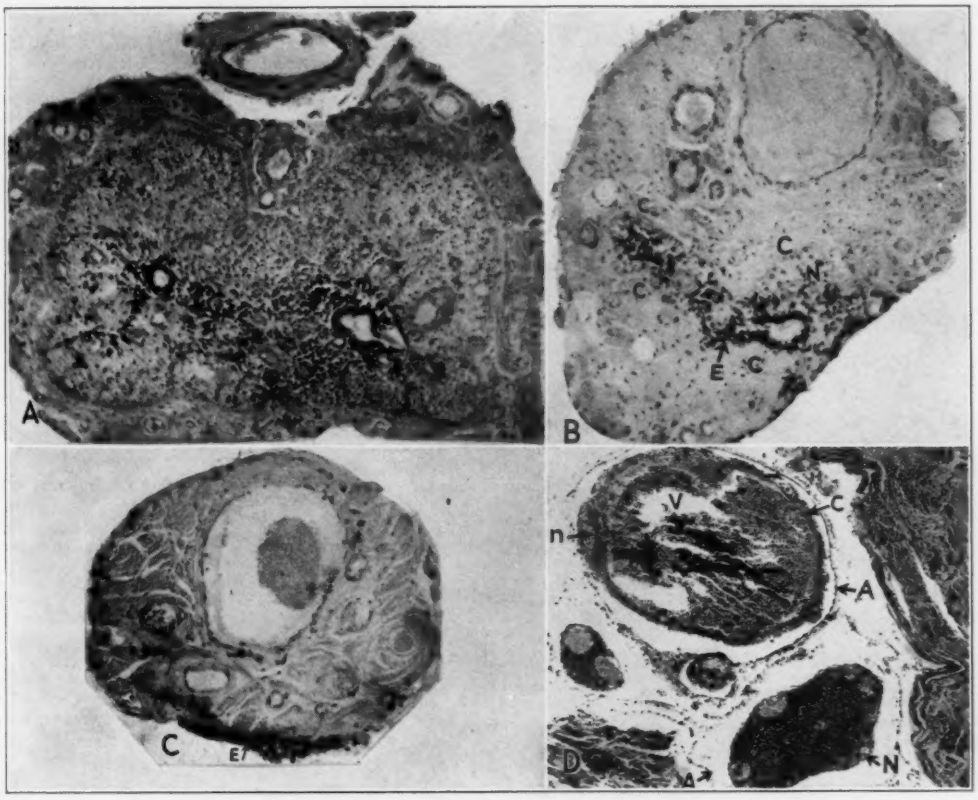

Fig. 3.—*A*, cross section through approximately the junction of the conus medullaris and the filum terminale, showing the double ependymal canal. Hematoxylin and phloxin stain; × 75. *B*, cross section through the midportion of the intradural part of the filum, in the approximate region of closure of the central canal. Note the prominent anterior spinal vein, the great thickening of the connective tissue sheath (*C*) and the decrease of neuroglia (*N*), the ependymal cells (*E*) becoming relatively more prominent among the interstitial tissue. Hematoxylin and phloxin stain; × 85. *C*, cross section of the intradural portion of the filum at approximately the junction of its middle and lower third. The interstitial tissue of the filum consists merely of ependymal cells (*E*) near the dorsal border of the filum. Hematoxylin and phloxin stain; × 100, *D*, cross section at the junction of the intradural and the extradural part of filum terminale. Note the prominent anterior spinal vein (*V*) surrounded by a connective tissue sheath (*C*), which contains a few small bundles of nerve fibers (*n*). Note also the arachnoid (*A*) covering the filum and the larger nerve bundles (*N*) and forming, peripherally, the perineurium. The dura mater (*D*) surrounds these structures and forms the epineurium peripherally. Hematoxylin and Van Gieson stain; × 60.

the lower regions of the filum a neuroglial stroma does not usually occur. Neuroglia cells have been encountered well below the first half of the filum, disappearing in one case 11 cm. from its origin. The intradural portion of the filum in this case was 14 cm. in length.

(*E*) Oligodendrocytes. Oligodendrocytes of the filum vary considerably in size, most of them being small. Their size depends directly

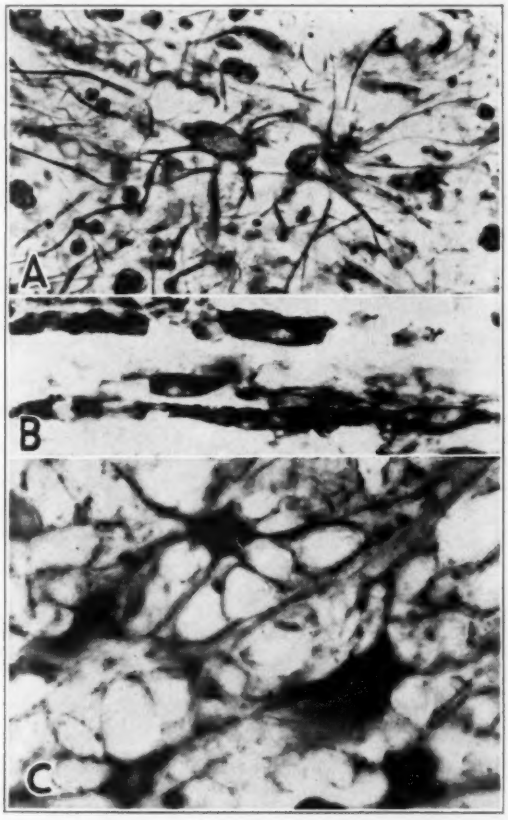

Fig. 4.—*A*, fibrous astrocytes of the conus medullaris. The same type of astrocyte occurs in the filum. Impregnation with lithium-silver carbonate (Rio Hortega's technic for astrocytes); × 430. *B*, oligodendrocytes along the nerve fibers of the upper half of the intradural portion of the filum terminale. Impregnation with silver carbonate (Dockrill's modification of Rio Hortega's technic); × 670. *C*, oligodendrocyte of the spinal cord enwrapping nerve fibers. The same type of oligodendrocyte occurs in the filum. Impregnation with silver carbonate (Dockrill's modification of Rio Hortega's technic); × 700.

on the caliber of the nerve fiber. They occur in rows covering the nerve fibers, as elsewhere along the fiber tracts (fig. 4 *B*). Other oligodendrocytes occur as satellites around nerve cells or in relation to blood vessels.

Their expansions wrap around the nerve fiber, forming a reticulated sheath (fig. 4 *C*). In the upper portion of the filum the rows of oligodendrocytes lie external to the central core of ependymal cells. Caudally, where ependymal cells occur more diffusely, rows or groups of oligodendrocytes are interspersed among them. Unless the oligodendrocytes are well impregnated, the differentiation of the two cell types may be difficult. The oligodendrocytes, like astrocytes and microglia cells, disappear usually within the first half of the intradural portion of the filum. In the region of transition to the peripheral portion of the filum, where neuroglia and microglia cells are replaced by Schwann cells and endoneurium, one sometimes sees a tendency toward an increase of oligodendrocytes, which recalls the piling up of cells along the course of certain cerebrospinal nerve roots.

(*F*) Microglia Cells. Microglia cells occur in the filum, as elsewhere in the central nervous system. They appear scattered here and there among neuroglia or ependymal cells.

(*G*) Connective Tissue. At the junction of the filum and the conus medullaris the connective tissue is represented by a somewhat thickened pial sheath. This sheath increases in size caudally. It is often thinnest dorsally, where it consists merely of a fine, pia-like membrane covering ependymal cells or neuroglia. The thickness of the connective tissue sheath varies considerably in subjects of the same age and height. In a case in which the diameter of the midportion of the intradural part of the filum measured 2 mm. (i. e., over twice that of the average filum terminale), the increase in size resulted from thickening of the connective tissue sheath. The blood vessels of this sheath often become increasingly prominent in the lower portion of the filum. The largest of these vessels is the anterior spinal vein, which in one case had undergone varicose enlargement to several times its normal size. The fibrous tissue of the sheath often sends septums into the filum, dividing its parenchyma into islands or columns of ependyma or neuroglia, through which the nerve fibers course. The connective tissue consists of heavy collagen fibers, although fine reticulin and a few elastic fibers occur. In addition to the usual connective tissue and endoneurial cells, one sees groups of fat cells among the bundles of fibrous tissue. Such fat is of the neutral variety, as indicated by the rose-colored reaction to nile blue sulfate.

The lumen of the connective tissue sheath more or less forms a V, with its apex directed caudally. Between the limbs of the V, which becomes increasingly thickened toward the apex, the nerve and interstitial structure of the filum is contained. The limbs of the V here and there present apertures for the passage of nerve fibers.

(*H*) Products of Degeneration. Various products of degeneration occur in the adult filum, becoming increasingly prominent with age. The most common are the corpora amylacea, which usually first appear in the marginal neuroglial layer. They frequently occur, too, along the fiber tracts among oligodendrocytes, astrocytes and nerve cells. Occasionally they are observed among ependymal cells and in the region of transition from the central to the peripheral segment of the filum. Several may coalesce, forming bodies of irregular size and shape. The amyloid bodies stain blue with hematoxylin and phloxin and varying intensities of purple with Rio Hortega's lithium-silver carbonate method. Round or irregular amorphous masses,[27] which stain reddish with lithium-silver carbonate and are usually larger than the amyloid bodies, may occur. Many of them are granular, lumpy or vacuolated. They sometimes occur in ependyma in relation to degenerating cells. Similar, although less densely staining, bodies, often finely granular or fibrillary, have been traced to their origin from degenerating reticulin balls. Such reticulin balls are derived from the connective tissue sheath of the filum, sometimes presenting narrow pedicles of attachment to the sheath. These balls of connective tissue, like the walls of blood vessels which are occasionally encountered, may undergo hyalinization in older subjects. Fragments of fibers or cells have been observed within or around some of these bodies, suggesting senile plaques. Vacuoles within cell bodies or along the fiber tracts of the filum occur too—amyloid may sometimes be faintly evident within these areas. Mucin was not revealed in any of the normal filums by mucicarmine stain.

2. Extradural Portion of the Filum Terminale: Clusters or sheets of cuboid cells, which are continuous with the arachnoid, may occur in the region of junction of the intradural and the extradural portion of the filum terminale. These cells project into the collagen stroma of the dura, which contains large, thin-walled blood vessels. The arachnoid surrounds bundles of nerve fibers and the central portion of the filum, finally being applied as a sheath with flattened lining cells. The groups of arachnoid cells become decreasingly conspicuous caudally and finally disappear. Just beyond this site the dura becomes applied to the bundles of nerves as the epineurium. Ultimately (usually within the first centimeter of the extradural portion of the filum), all bundles of nerve fibers acquire a perineurium and an epineurium. Psammoma bodies occur in older subjects in the region of junction of the two portions of the filum.

Bundles of nerve fibers of various sizes form a conspicuous feature of the upper extradural portion of the filum. They become less

27. Occasional amorphous masses were encountered in the filum of a newborn infant, but their origin could not be determined.

prominent caudally, migrating laterally to their foramens of exit. Non-myelinated fibers occur among these bundles in varying proportions.

Around the filum there is often an abundance of fat, which may fill the vertebral canal in this region. The amount of fat within the filum and around it varies considerably in different persons. Finally the extradural portion of the filum fuses with the dense fibrous tissue of the

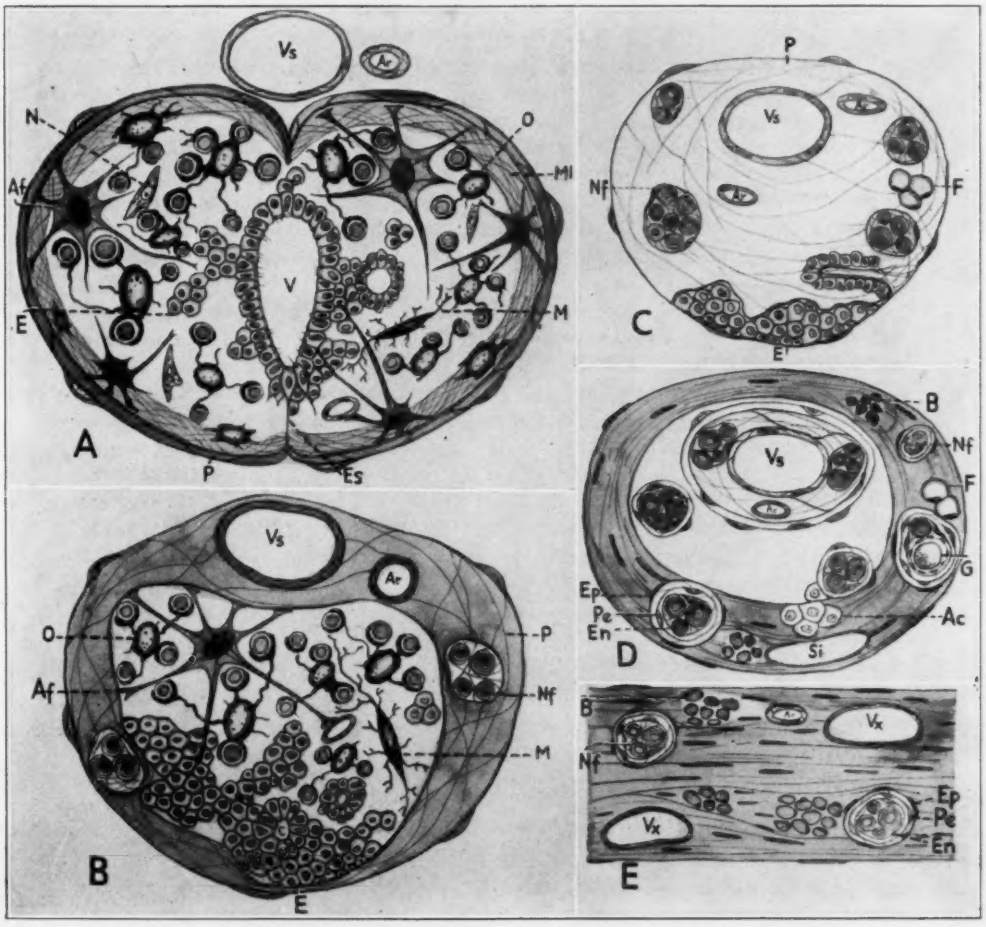

Fig. 5.—Diagrams of cross sections of the filum terminale. *A* represents the middle portion of the ventriculus terminalis; *B*, a level near the site of closure of the central canal of the filum; *C*, a level near the site of disappearance of the ependyma, and *D*, the site of transition from the intradural to the extradural portion of the filum terminale. Note that the bundles of nerve fibers in the connective tissue sheath of the filum (and, similarly, those in the subarachnoid space) are surrounded by endoneurium; those in the subdural space have, in addition, a perineurial sheath, while those in the dura have a third connective tissue sheath, the epineurium. *E* shows fusion of the extradural portion of the filum terminale with the periosteum of the coccyx. For interpretation of the lettering, see the legend accompanying figure 6.

EXPLANATION OF FIGURE 6

Fig. 6.—Diagram of the filum terminale and its transition from the lower end of the spinal cord. The interrelationships between the lengths of the various segments are preserved. *A* represents the arachnoid, with sheets of cells (*Ac*) surrounding the nerve or extending into the dura; *Ap*, a protoplasmic astrocyte; *Af*, a fibrous astrocyte; *Ar*, an artery (fig. 5); *B*, bundles of collagen fibers seen in cross section (fig. 5); *C*, the central canal; *Cx*, fusion of the extradural portion of the filum and the periosteum of the coccyx; *D*, the dura mater; *De*, elastic tissue of the dura; *E*, ependymal cells, some of which contain cilia and blepharoplasts and at times form rings around clear canals, blood vessels or projections of connective tissue; *En*, the endoneurial sheath with endothelial cells; *Eo*, other cells of the endoneurium—a fibroblast, a clasmatocyte (with granules in the cytoplasm) and a wandering (round) cell; *Ep*, the epineurium; *Es*, an ependymal spongioblast; *F*, fat cells in the connective tissue of the intradural and extradural portions of the filum; *G*, ganglion cells along the course of nerve fibers within and around the filum; *M*, microglia cells; *Ml*, the marginal neuroglial layer; *N*, nerve cells, the absence in the fourth sacral segment of the large lateral horn cells of the third, diminution of nerve cells in the coccygeal segment and occurrence of occasional ganglion cells in the first 3 cm. of the filum being indicated, *Nf*, nerve fibers in bundles, in which nonmyelinated fibers are indicated by three circles and myelinated fibers by four circles, denoting the axis-cylinder, myelin sheath, sheath of Schwann and endoneurial sheath (fig. 5); *Nr*, nerve roots of the third, fourth and fifth sacral and the first coccygeal segments; *O*, interfascicular oligodendrocytes, ensheathing nerve fibers; *Os*, satellite oligodendrocytes; *P*, the pia mater forming the sheath for the filum, with increase in connective tissue caudally; *Pe*, the perineurium; *S*, Schwann cells with π or protagon-like granules, occurring along a medullated nerve fiber; *Si*, a sinusoid of the dura (fig. 5); *Sw*, Schwann cells without π granules, occurring along a nonmedullated nerve fiber; *T*, transition from the intradural to the extradural portion of the filum; *V*, the ventriculus terminalis; *Vs*, the anterior spinal vein, and *Vx*, veins of the extradural portion of the filum and the periosteum (fig. 5).

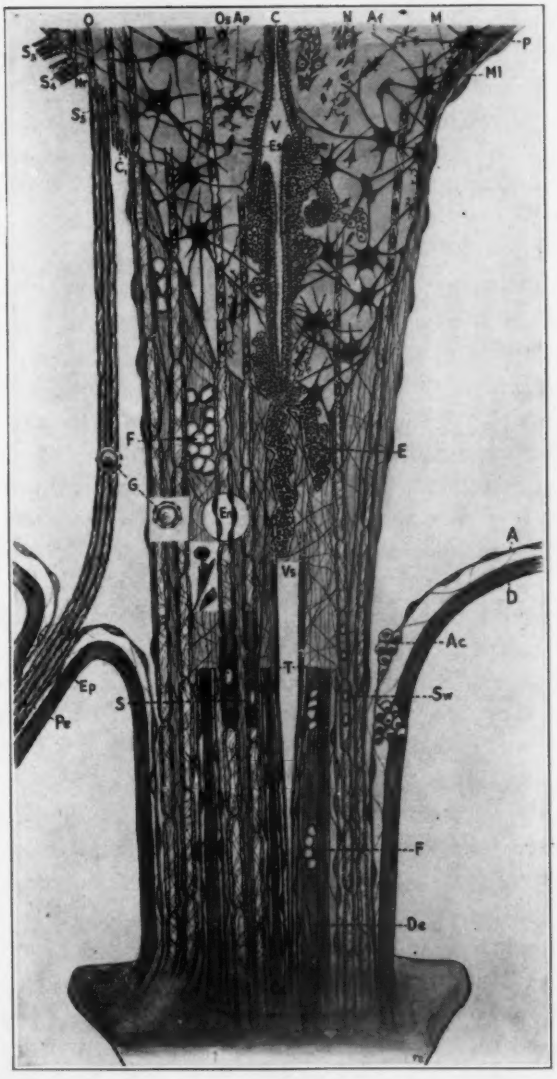

Figure 6

periosteum on the back of the coccyx, to which it is attached. Fibrous attachments to the periosteum over the lower portion of the sacrum, too, may exist. Small bundles of nerve fibers with characteristic endoneurium, perineurium and epineurium occur along the entire filum, continuing to the periosteum of the coccyx. The epineurium of these nerves is part of the surrounding dense connective tissue derived from the dura mater, and often cannot be distinguished as a separate structure. The anterior spinal vein, which occurs conspicuously along the ventral surface of the intradural part of the filum, may appear along much of the course of the extradural portion, although it is often invisible through the thick connective tissue sheath.

COMMENT

The small nerve cells encountered in the upper portion of the filum probably correspond to the cells which have been called neuroblasts. The fact that similar cells occur at all levels of the adult spinal cord and in the brain indicates that they may be mature cells rather than neuroblasts. The occurrence of these cells within the ependyma probably is the result of retardation in migration from the internal limiting membrane, most of the nerve cells reaching a position peripheral to the ependymal layer. The occurrence of ependymal cells opposed to the connective tissue of the filum is an unusual condition in the normal adult human nervous system. Elsewhere the processes of astrocytes form the barrier. Such a disposition of the ependyma occurs normally in some lower vertebrates. The tailed cells of the filum correspond to the cells which Cajal [28] described in certain portions of the mammalian spinal cord, and which are more commonly seen in invertebrates. They represent ependymal or primitive spongioblasts.

Degenerative changes frequently occur in the filum, being more prominent there than in most regions of the central nervous system. Many amorphous masses encountered suggest the *Heerde* described by Thomsen [29] and others in the cerebrospinal nerve roots, which are believed to arise from ganglion cells as a result of degeneration. It is likely that they may arise from various structures, since some contain fragments of ependymal cells; other bodies, which are less dense and homogeneous, result from degeneration of reticulin balls. The occurrence of degenerative changes in the cells bordering the lumen of ependymal canals suggests the mechanism for enlargement of these

28. Ramón y Cajal, S.: Histologie du système nerveux, Paris, A. Maloine, 1901, vol. 1.

29. Thomsen, R.: Ueber eigenthümliche aus veränderten Ganglienzellen hervorgegangene Gebilde in den Stammen der Hirnnerven des Menschen, Virchows Arch. f. path. Anat. **109**:459, 1887.

rings, which vary so greatly in size. Such a mechanism for enlargement of the ependymal canals recalls that observed by Streeter in the development of the ventriculus terminalis—"retrogressive thinning out of the walls of the spinal cord with a consequent enlargement of the central canal."

The functional significance of the nerve fibers in the filum is of interest for further investigation. Uenae,[30] as a result of degeneration experiments with cats, supplied evidence that the filum terminale contains ascending fibers which reach the nuclei of the columns of Goll in the medulla oblongata through the posterior columns.

There is an analogy between the structure of the filum terminale and that of a nerve root in that nerve fibers in each undergo transition from a central glial to a peripheral nonglial ensheathment. In this respect they present central and peripheral segments. Also, in both the filum and the nerve root there is sometimes a tendency toward piling up of cells at the transition zone. These phenomena, however, are more difficult to ascertain in the case of the filum, since longitudinal sections of the relatively scant nerve fibers which show their transition are not readily obtained. The nerve fibers of the filum pierce a connective tissue structure which might be considered analogous to the pial ring of the cerebrospinal nerve roots. However, since the pia at this site has undergone marked thickening, a definite pial ring derived from the inner layer of the pia, such as exists on the nerve roots, could not be determined. Both structures become surrounded by peripheral reflections derived from all three layers of the meninges. From the embryologic point of view the analogy between the filum terminale and a nerve root does not hold strictly, since the phenomenon of dedifferentiation enters into the development of the filum.

Prof. Wilder Penfield and Asst. Prof. William Cone offered suggestions in this study, and Miss F. Bechman made the drawings.

30. Uenae, F.: Ueber die aufsteigenden Fasern im Filum terminale der Katze, Acta scholae med. univ. imp. in Kioto **13**:409, 1931; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **61**:692, 1931-1932.

ENCEPHALOGRAPHIC FINDINGS IN CASES OF ATHETOSIS AND RELATED DISORDERS

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AND
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Since the introduction of surgical methods of treatment of athetosis and related diseases [1] the problem of precise and definite diagnosis has become an important one. Encephalography has therefore been performed in a series of 13 cases of the athetoid syndrome in one or another form, in most of which the patient was a candidate for operation. The results have been compared with the findings in 2 cases in which also chordotomy was done and in which on review the disease appears to belong in a different category. Observations were also compared with those in a group of 6 cases of various conditions in which the encephalographic appearance resembled that seen in cases of the athetoid syndrome but in which abnormal movements did not occur.

There are comparatively few records of the results of encephalography in cases of this type. Goodhart, Balzer and Bieber [2] reported 3 cases of Wilson's disease, 3 of dystonia, 4 of double athetosis and 5 of Little's disease. They stated that in the cases of athetosis and in 2 of the cases of dystonia the encephalograms were normal. In 1 case of dystonia there were diffuse cortical atrophy and dilatation of the cisterna ambiens. In the cases of Little's disease there were hydrocephalus and porencephaly.

DEFINITION OF THE ATHETOID SYNDROME

The classification of the commoner diseases characterized by abnormal involuntary movements on the basis of the results of section of the extrapyramidal tracts and of data acquired by electromyographic studies has been considered in another paper.[1] In brief, it has been

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1. Putnam, T. J.: Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Psychiat. **39**:258 (Feb.) 1938.

2. Goodhart, S. P.; Balzer, B. H., and Bieber, I.: Encephalographic Studies in Cases of Extrapyramidal Disease, Arch. Neurol. & Psychiat. **35**:240 (Feb.) 1936.

suggested that a group of dyskinetic diseases, in all of which the symptoms appear to be produced by similar physiologic mechanisms, have the following features in common:

1. The abnormal movements are slower than most voluntary movements; they affect sometimes one, sometimes another, group of muscles; contraction is maintained or altered slowly once it occurs, and gives rise to gross, usually varied, movements of the extremities and trunk.
2. Any portion of the musculature may be involved. Grimacing, torticollis, dystonia and athetosis may all be present in a single case, with or without alterations of the reflexes.
3. Electromyographic records show irregular waves of impulses, sometimes of peculiar pattern but entirely devoid of the rhythmicity characteristic of cerebellar disease, paralysis agitans and clonus.
4. Encephalograms often show the deformities to be described later in detail.
5. The symptoms persist with large doses of hypnotic drugs and are little affected by scopolamine and similar substances.
6. The abnormal movements are ameliorated to a greater or lesser degree by section of the anterior quadrant of the spinal cord.

The term "athetoid syndrome" is suggested as appropriate for conditions meeting most of the criteria enumerated. Wilson's and Sydenham's chorea, myoclonus and paralysis agitans are specifically excluded from the group.

Since a review of the essential clinical features in the majority of cases reported has already been given elsewhere,[1] they will be described only briefly here. The syndrome appeared to result from birth injury in 9 of the 13 cases. In 1 case it followed a vascular accident occurring during an acute infection. No etiology was obvious in the remaining 3 cases. The symptoms were bilateral in 5 cases and unilateral in the rest. In 3 cases in which the symptoms were bilateral the neck and shoulders were involved more than the legs. In all the cases in which there were only unilateral symptoms the arm was most severely involved, and the neck and face were spared.

METHOD OF ENCEPHALOGRAPHY

The technic employed in most of the cases was that which has been reported elsewhere;[3] it aims at complete filling of the subarachnoid spaces, and roentgenograms are taken with the head erect. All lateral and some anteroposterior roentgenograms were stereoscopic. The quality of the pictures varied somewhat, but only those in which the ventricles and cisterns were clearly outlined were accepted for the series.

3. von Storch, T. J. C.: On the Technique of Encephalography, with Special Reference to the Use of Apparatus, Am. J. Roentgenol. **35**:78, 1936.

ENCEPHALOGRAPHIC FINDINGS IN CASES OF ATHETOSIS

Certain abnormalities were observed with considerable regularity in cases of the athetoid syndrome, though sometimes one or another might be lacking or questionable. In all cases one or both lateral ventricles were enlarged. In cases in which the symptoms were unilateral the contralateral side regularly showed greater atrophy. This, however, was a banal and nonspecific abnormality and slight in some instances. More important for differential diagnosis was the depression of the floor of the affected ventricle, due apparently to atrophy of the basal nuclei. Some degree, often slight, of this downward enlargement was observed in all but 3 of the cases.

E. S., a girl aged 15, was admitted to the hospital on Sept. 18, 1936. One sister is epileptic; one died of diabetes; the mother had diabetes. The past history was noncontributory except that of birth. After an instrumental delivery there developed a contracture of the right wrist and hand. There were definite, but minimal, choreoathetoid movements in the hand and wrist, with complete disability.

Examination showed hyperflexion of the wrist, with hyperextension and spasticity of the fingers. An electromyogram showed rapid bursts of impulses in this extremity. Mentality was normal.

Encephalograms showed a normal right lateral ventricle, with slight enlargement of the left lateral horn, especially the posterior third. The floor of the left lateral ventricle was depressed and the third ventricle somewhat enlarged, especially to the left (fig. 1). The basal cisterns were slightly larger than normal. There was no evidence of cortical atrophy.

Since the case was considered one in which there was a marginal chance for benefit from operation, the anterior column and prepyramidal tract on the right were sectioned at the second cervical segment. Operation and recovery were uneventful, but the results were disappointing with regard to return of function.

The next most constant abnormality was lateral enlargement of the third ventricle. Of the eleven sets of plates in which the third ventricle was clearly outlined in the anteroposterior position, the greatest transverse diameter measured from 6 to 15 mm. in all but one, that in the case of a child aged 8½ years with mild bilateral symptoms, in which it measured 4 mm. In cases in which there were unilateral symptoms the enlargement was directed predominantly or wholly toward the contralateral side. As with the other deformities, the extent of the atrophy was roughly proportional to the symptoms, and in some cases was slight.

J. K., a boy aged 16 years, was admitted on March 9, 1935. Delivery was stated to have been normal, but the patient received an injury to the head at the age of 1 year. A year later involuntary movements of the right arm and leg began and increased steadily. There was slight mental retardation.

The right arm was in a constant state of slow motion of considerable amplitude, so that the patient usually had to hold it with the left hand. The arm

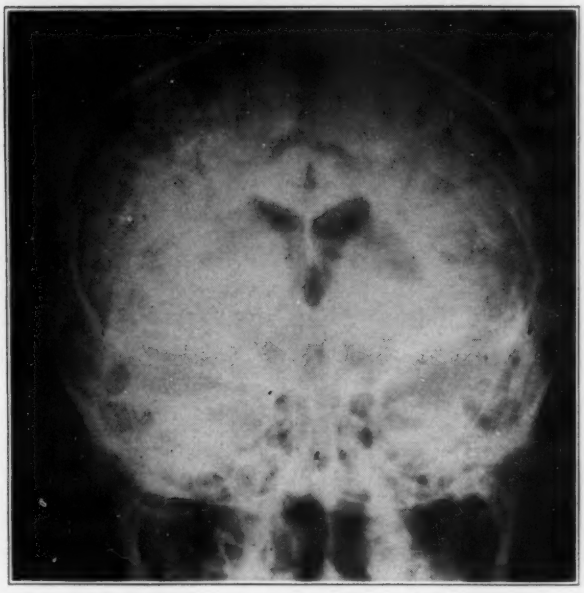

Fig. 1 (case 1).—Anteroposterior roentgenogram. The left lateral ventricle is slightly enlarged, chiefly at the expense of basal structures. The third ventricle is also enlarged to the left.

Fig. 2 (case 2).—Anteroposterior roentgenogram. The left lateral ventricle is enlarged slightly, chiefly downward. The third ventricle is distinctly enlarged to the left.

was entirely useless. The deep reflexes were increased on the right, but there was no Babinski phenomenon.

Encephalograms showed that the left lateral ventricle was enlarged, chiefly anteriorly, as compared with the right, which appeared normal. The enlargement affected the floor of the ventricle considerably more than the roof and walls (fig. 2). The third ventricle was enlarged to the left, measuring 10 mm. in transverse diameter. The basal cistern was definitely enlarged, as was the fourth ventricle. There was some atrophy of the frontal cortex on the left side.

At operation the right anterior column and prepyramidal tract were severed at the second cervical segment. The patient was entirely relieved from athetoid movements for about four months. They then returned to some extent, but were far less than before operation.

Finally, enlargement of the basal cistern was observed in most instances. In 6 cases the enlargement was definite and striking; in the rest it might be questioned. It is difficult to lay down definite criteria of abnormality. The greatest anteroposterior measurement (juncture of the pons and peduncles with the supraoptic recess) varied from 30 to 35 mm.; certainly, the lower figure is above the normal average. The vertical diameter also appeared to be increased in a few instances; it was difficult, however, to find fixed points to measure.

M. G., a man aged 56, whose history has been reported in detail elsewhere,[1] had suffered from extremely severe bilateral athetosis and torticollis since the age of about 20. Mentality was high normal, and there were no signs of involvement of the pyramidal tract.

Encephalograms (by permission of Dr. Robert S. Schwab) showed enlargement of both ventricles involving the left more than the right and the anterior portion more than the posterior. There was slight depression of the floor of both ventricles, greater on the right. Cortical atrophy was minimal. The third ventricle measured 14 mm. in transverse diameter. The basal cistern was strikingly enlarged, measuring 35 by 13 mm.

Operation was performed, but the patient died a week later, of pulmonary atelectasis and cardiac failure. Autopsy showed diffuse atrophy of the cells of the lenticular nuclei.

To illustrate the less common situation in which vertical enlargement of the basal cistern takes place, the following case may be cited.

C. L., a feebleminded girl aged 10, who was born prematurely, showed abnormal movements during the first year of life. They grew progressively worse, so that at the time of admission to the hospital, on Nov. 14, 1935, she could not lie still in bed or talk, and sitting up, feeding herself or walking was out of the question.

Examination revealed little of importance except the continuous movement of all extremities and the neck, face and tongue. The deep reflexes were not particularly active, and there was no Babinski phenomenon.

Encephalograms showed that both lateral ventricles were markedly enlarged, the left more than the right. The floor of both ventricles was depressed, and the third ventricle was widened to 9 mm. The roof of the basal cistern was exceptionally high (fig. 4). There was no evidence of cortical atrophy.

Fig. 3 (case 3).—Lateral view. The ventricles are only slightly enlarged; the basal cistern is markedly enlarged.

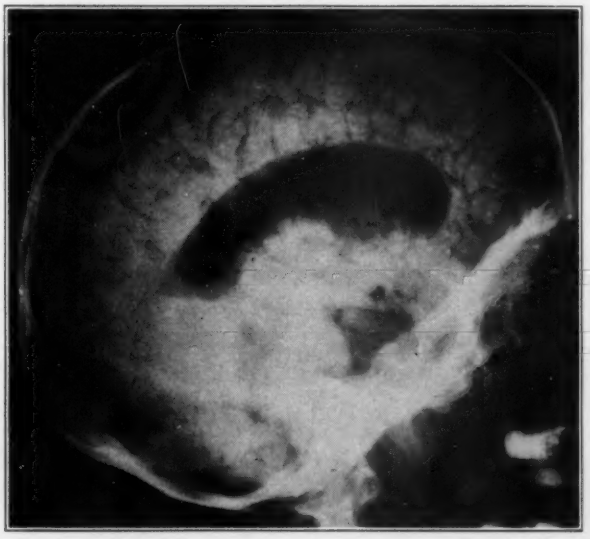

Fig. 4 (case 4).—Lateral view, showing elevation of the roof of the basal cistern, and definite enlargement of the lateral ventricles.

At operation the first three cervical anterior roots, the spinal accessory nerves on both sides and the right anterior column at the second cervical segment were cut. The patient was considerably improved and could lie quietly in bed, which had previously been impossible.

Defects of other types, such as scattered areas of cortical thinning, are occasionally observed. In 1 case there was cleancut atrophy of the region of the precentral gyrus; yet the athetosis of the contralateral hand was similar to that in other cases in the series. There were no signs of deficit of the pyramidal tract except a Babinski reflex, and the patient had relief and good voluntary motion after operation. In no instance was there evidence of particular damage to the premotor cortex.

ENCEPHALOGRAPHIC CHANGES ACCOMPANYING OTHER DYSKINETIC DISEASES

C. K., a man aged 21, who was referred by Dr. Merrill Moore and admitted on July 15, 1935, had been well until the age of 10. At that time he had a febrile illness characterized by drowsiness, and since there had gradually developed severe tremor, involving both arms and the neck and face, whether the patient was at rest or in motion. In addition, he was subject to frequent attacks of tossing the head, blinking the eyes and dropping the lower jaw. Intelligence was distinctly below normal. There was little rigidity.

Encephalograms showed slight enlargement of both lateral ventricles, the left being larger than the right. The third ventricle was dilated slightly to the left and measured 10 mm. in transverse diameter. The basal cistern was somewhat enlarged. There was no evidence of cortical atrophy.

Section of the two anterior columns was performed at the second cervical segment on one side and the third cervical segment on the other. The patient made a good recovery, but the abnormal movements were not in the least affected.

In view of the history of what may well have been encephalitis, the alternating tremor without mobile spasm and the absence of good results from operation, it was considered that this case was not one of the athetoid syndrome but presumably an example of scattered postencephalitic lesions, some of which involved the superior cerebellar peduncle and the hypothalamic nuclei. In such cases atrophy of the basal nuclei and the upper portion of the brain stem is seen post mortem, which may grossly resemble the abnormalities seen in athetosis (Hertz [4]).

B. G., a girl aged 15, who was referred by Dr. Nicholas Ransohoff, of New York, was admitted on Oct. 12, 1935. She had apparently sustained an injury at birth, and there had gradually developed spontaneous movements of the right arm, of increasing severity. The movements were coarse, alternating and equally

4. Hertz, E.: Die amyostatischen Unruheerscheinungen: Klinisch-kinematographische Analyse ihrer Kennzeichen und Begleiterscheinungen, J. f. Psychol. u. Neurol. **43**:3, 1931.

severe whether the patient was at rest or giving attention. They were not associated with rigidity. There was a Babinski sign bilaterally; neurologic examination otherwise gave essentially normal results. Intelligence was normal.

Encephalograms showed poor filling. The lateral ventricles did not appear enlarged; the third ventricle measured 2 mm. in transverse diameter, and the basal cistern was within normal limits (measuring 25 by 12 mm.). Thus, no definite abnormalities were demonstrated.

The right anterior column was severed at the second cervical segment. There was no change in the movements after operation.

In this patient, also, the character of the alternating movements and the lack of improvement after operation suggest that the syndrome rests on a physiologic basis different from that of athetosis.

EVIDENCES OF ATROPHY OF BASAL STRUCTURES IN CONDITIONS NOT ACCOMPANIED BY ABNORMAL MOVEMENTS

The changes which have been described as characteristic of athetosis may also occur in other conditions. Of a group of approximately fifty sets of roentgenograms, six showed definite diencephalic atrophy with depression of the floor of the lateral ventricles, excavation of the third ventricle toward the affected side and enlargement of the basal cistern. In 4 cases there occurred convulsions; in 1, post-traumatic headache, and in 1, a peculiar form of "encephalitis" with mental deterioration and spasticity. In all there were marked enlargement of the lateral ventricles and usually cortical atrophy. While there occurred abnormalities of the various types described, they were far less marked as compared with the diffuse atrophy of the brain as a whole than those in the cases of athetosis. However, the encephalographic studies are not in themselves diagnostic of athetosis.

USE OF ENCEPHALOGRAPHY IN CASES OF ATHETOSIS

The question may well be raised: What is the practical value of encephalography in cases of athetosis? The procedure is usually not essential in making the diagnosis, and it does not afford absolute differentiation from other conditions causing enlargement of the ventricles, or even from some accompanied by other types of dyskinesia. It may, however, have two uses. First, in a case in which there are abnormal movements and hysteria is suspected—and this occurred in 2 cases in the present series—encephalography may establish the presence of organic disease. Second, it may indicate the amount of residual defect to be expected after operation, as patients with severe bilateral lesions are apt to have far less voluntary function, even if the athetosis is alleviated, than those with changes largely confined to the basal nuclei.

SUMMARY

1. In a series of 13 cases of athetosis and dystonia encephalography has been performed. Certain changes appear with considerable constancy in the roentgenograms. They include: enlargement of one or both ventricles, especially at the expense of the floor of the ventricle, enlargement of the third ventricle in a direction away from the clinically affected side and enlargement of the basal cistern.

2. Similar changes are occasionally seen in other conditions characterized by enlargement of the ventricles. In general, however, in the cases of athetosis the basal atrophy is more marked as compared with the size of the ventricles and the cortical atrophy than it is in other diseases.

3. Indications for employment of encephalography in relation to diagnosis, prognosis and operation are discussed.

SWEAT SECRETION IN MAN

II. ANATOMIC DISTRIBUTION OF DISTURBANCES IN SWEATING ASSOCIATED WITH LESIONS OF THE SYMPATHETIC NERVOUS SYSTEM

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AND

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In a previous investigation [1] the sweat secretion of normal persons was studied with the aid of Minor's iodine and starch method. It was pointed out that sweat is secreted under the influence of the nervous system, in particular under that of the thoracolumbar portion of the sympathetic system. Hence, the sweating test is one of the most valuable objective methods of analyzing the sympathetic cutaneous innervation. There are several procedures by which sweating may be induced, but it was shown that for the study of sympathetic function only the "thermoregulatory" sweating produced by the application of external heat and the ingestion of fluids and acetylsalicylic acid give reliable and conclusive results.[2]

Before the sweating reactions are described, a review of the general anatomic relations of the sympathetic chain and its connections is necessary.[2d] According to the conception of Gaskell [3] and Langley,[4] the sympathetic system consists of two sets of neurons.[5] The cell of the first neuron is situated in the intermediolateral column of the spinal cord (between the first dorsal and the third lumbar segment). The

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1. List, C. F., and Peet, M. M.: Sweat Secretion in Man: I. Sweating Responses in Normal Persons, Arch. Neurol. & Psychiat. **39**:1228 (June) 1938.

2d. The sympathetic connections with visceral organs are not considered here. Schweisssekretion, Ztschr. f. d. ges. Neurol. u. Psychiat. **116**:504-536, 1928. (*b*) Guttmann, L.: Die Schweiss-sekretion des Menschen in ihren Beziehungen zum Nervensystem, ibid. **135**:1-48, 1931. (*c*) List, C. F.: Studies of Sweat Secretion in Man, Univ. Hosp. Bull., Ann Arbor **2**:40, 1936.

2d. The sympathetic connections with visceral organs are not considered here.

3. Gaskell, W. H.: The Involuntary Nervous System, London, Longmans, Green & Co., 1916.

4. Langley, J. N.: The Sympathetic and Other Related Systems of Nerves, in Schäfer, E. A.: Textbook of Physiology, London, Y. J. Pentland, 1900, vol. 2.

5. This conception, although criticized by opponents of the neuron theory (Stoehr Jr.), gives a satisfactory explanation of physiologic and clinical problems.

medullated axon of this cell, which was called the preganglionic fiber by Langley and the connector fiber by Gaskell, passes via an anterior root and a white ramus to a ganglion of the sympathetic chain. The cell of the second neuron lies in the sympathetic ganglion. Its non-medullated axon leaves the chain, traveling via a gray ramus to a mixed radicular nerve. This is the so-called postganglionic fiber of Langley, or the effector fiber of Gaskell. In the peripheral nerves the post-ganglionic sympathetic fibers accompany the sensory cerebrospinal fibers in their course to the skin. Each gray ramus distributes its post-ganglionic fibers approximately to the same cutaneous area as that supplied with sensory fibers by the corresponding radicular nerve. In other words, the segmental postganglionic innervation closely corresponds with the sensory dermatomes. The preganglionic supply in a white ramus, however, does not correspond to a sensory segment but covers a much wider cutaneous area. According to Ranson and Billingsley,[6] each preganglionic fiber synapses with the cell bodies of many second neurons, which are distributed over several ganglia of the chain.

Similar to the sensory innervation of the skin, the sympathetic innervation shows considerable overlapping of fibers supplying adjacent cutaneous areas. This overlapping is more marked in the areas of radicular than in those of peripheral innervation. As in cases of lesions of peripheral nerves, the area of sensory loss is always smaller than the actual anatomic distribution of the severed nerve, so the area of anhidrosis is smaller than would be expected on anatomic grounds. This is due to the fact that only the central part of the area of anatomic distribution is innervated by the sectioned nerve alone (autonomous area), whereas in the peripheral (subsidiary) zone overlapping by the intact neighboring nerves reduces the extent of functional loss. Therefore, it seems a sounder principle to observe the function which remains after a certain portion of the sympathetic nervous system has been removed than to draw conclusions from the extent of functional loss. This point of view will be stressed in the clinical observations which follow.

SYMPATHETIC INNERVATION OF THE HEAD AND NECK

The sympathetic fibers for the head and neck arise in the cervical portion of the sympathetic chain. The cervical portion ordinarily exhibits three ganglia: the superior, the middle and the inferior cervical ganglion. The superior cervical ganglion is formed by fusion of the upper four cervical ganglia; the middle ganglion, by fusion of the fifth and sixth cervical ganglia and the inferior, by fusion of the seventh

6. Ranson, S. W., and Billingsley, P. R.: Studies on the Sympathetic Nervous System, J. Comp. Neurol. **29**:305-312, 1918.

and eighth cervical ganglia. The middle cervical ganglion, however, is inconstant and may be absent. In this case it is fused either with the superior or with the inferior ganglion. The inferior ganglion usually is united with the first dorsal ganglion, thus forming the so-called stellate ganglion. Most fibers of the cervical portion of the sympathetic chain are ascending. All of its preganglionic fibers originate in the cells of the intermediolateral column of from the first to the fourth thoracic segment and pass through the corresponding anterior roots and white rami into the chain, traveling in a cephalad direction. There is great variation in the course of the gray rami. The postganglionic fibers of the superior cervical ganglion supply the ipsilateral side of the head and the first three or four cervical cutaneous segments. If a lesion is located above the superior cervical ganglion, the fibers for the head only are interrupted. If the lesion is situated below the middle cervical ganglion, the fibers for the fourth, fifth and sixth cervical segments are also interrupted. If the middle cervical ganglion is absent, the gray rami for the fifth and sixth, and occasionally also the fourth and seventh, cervical nerves may arise directly from the sympathetic trunk. These anatomic deductions will be illustrated by 5 clinical cases.

Case 1.—R. J. complained of severe pain, of a migrainous type, involving the right side of the face and scalp. The right superior cervical ganglion was resected. After operation the pain was relieved, but not abolished. There was a complete Horner syndrome on the right. The sweating test with application of heat revealed an area of anhidrosis extending over the right side of the face and the upper portion of the neck down to the second cervical segment. A zone of hyperhidrosis corresponding approximately to the borderline of the third and fourth cervical segments was noticed at the beginning of the test, but later became less conspicuous.

Case 2.—L. B., ten days previously had had resection of the left superior cervical ganglion for relief from angina pectoris. A complete Horner syndrome was present on the left. The sweating test (fig. 1 *A* and *B*) showed an area of complete anhidrosis covering the entire left side of the head and the upper part of the neck. The borderline corresponded approximately to the lower limit of the second cervical segment.

Case 3.—H. C. K., gave a history of typhoid three years ago, with gradual development of the Horner syndrome on the right side. This was the only abnormal neurologic finding. Spontaneous sweating was visible over the left side of the nose and upper lip and the left cheek. The sweating test (fig. 1 *C*) demonstrated complete anhidrosis on the right side of the face to the level of the second cervical segment. There was marked hyperhidrosis over the right side of the neck, the right shoulder and the proximal portion of the upper part of the right arm.

It is not surprising that after extirpation of the superior cervical ganglion anhidrosis is confined to the face and the first two cervical segments, although the superior cervical ganglion supplies also the third, and even the fourth cervical segment with communicant rami. It must be remembered that the intact middle cervical ganglion or the inter-

ganglionic portion of the trunk also sends branches to the third and fourth cervical segments. In some cases even the inferior cervical ganglion may have connections up to the fourth cervical nerve (Hovelacque [7]). These fibers apparently permit the maintenance of function in the third and fourth cervical segments. The longer the

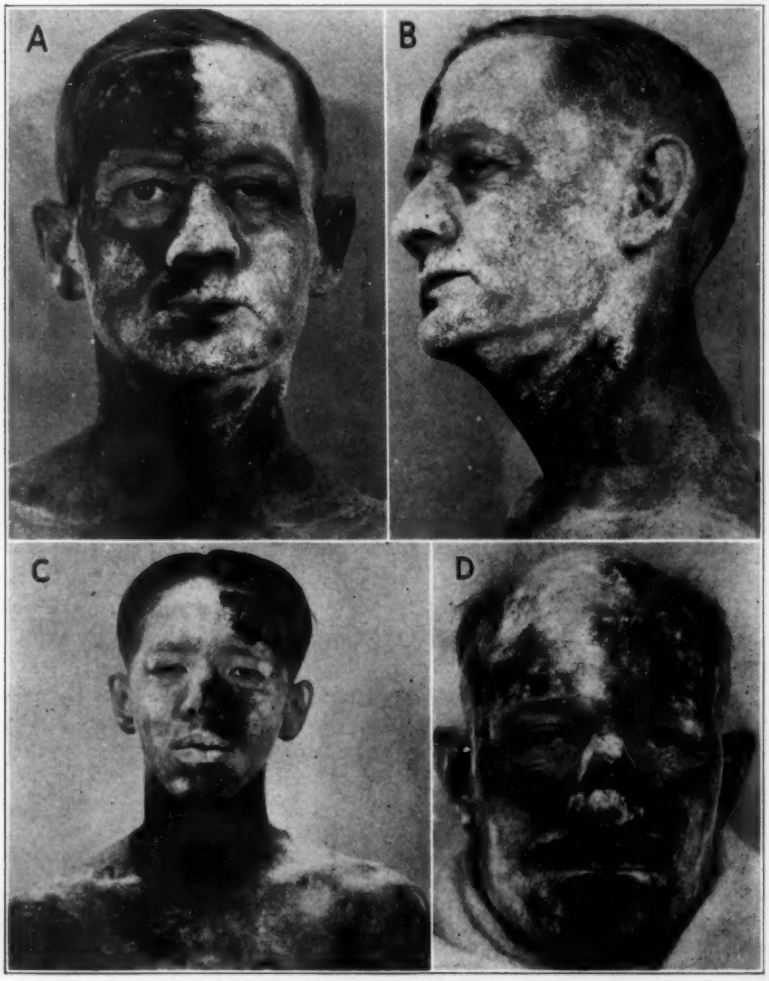

Fig. 1.—*A* and *B* (case 2), resection of the left superior cervical ganglion; *C* (case 3), lesion of the right superior cervical ganglion, with "perilesionary" hyperhidrosis of the neck, shoulder and upper part of the chest on the right side, and *D* (case 4), lesion of the right internal carotid plexus.

7. Hovelacque, A.: Les rameaux communicants du sympathique cervical, Ann. d'anat. path. **1**:605-616, 1924; Le sympathique du membre supérieur, ibid. **6**:968-998, 1929.

period that has elapsed after the operation the more complete is the functional control which the subsidiary fibers of the middle cervical ganglion exert over the territory of the third and fourth cervical segments. After complete removal of the superior cervical ganglion no anatomic regeneration occurs. This was borne out by the statement of a patient who had a superior cervical sympathectomy twenty-two years before for relief from exophthalmic goiter. The patient observed that the denervated side of the face remained dry during the hot summer months while the other side sweat profusely. (Unfortunately, this patient could not be examined by the sweating test.)

In some cases the area of anhidrosis was surrounded by a zone of hyperhidrosis. This so-called perilesionary hyperhidrosis is apparently a compensatory phenomenon, indicating a condition of irritation in the nerves or sweat glands adjacent to the lesion. Thus, in case 1 the area of "perilesionary" hyperhidrosis served as a better landmark for the actual extent of the lesion than did the zone of complete anhidrosis. In case 3 the "perilesionary" hyperhidrosis was particularly striking and involved the whole territory supplied by the middle cervical ganglion and a part supplied by the inferior cervical ganglion.

If the lesion involves the cranial end branches of the cervical portion of the sympathetic trunk, the loss of sweating may cover only a small area, as demonstrated by the following case.

CASE 4.—C. I., for about thirty years had complained of occasional headaches, lasting for from six to eight hours. The pains usually occurred on the right side, rarely on the left. They started in the occipital region and radiated to the temple, forehead and eye. At the height of an attack marked lacrimation and congestion of the conjunctiva occurred on the right side. Furthermore, tactile hyperesthesia of the right frontal and anteroparietal areas was noted. There was nerve any nausea, vomiting or ophthalmic phenomena (scintillating scotoma, amaurosis or diplopia).

Examination showed slight, but definite, sympathetic ptosis and marked pupillary miosis on the right side. The reactions of both pupils to light and in accommodation were normal and equal, but the ciliospinal reflex was sluggish and diminished on the right and active on the left. Sensation over the entire area of the trigeminal nerve was normal and equal for all qualities, as were the corneal reflexes. Intraocular tension was normal, being 19 mm. on the right and 22 mm. on the left. The fundi showed moderate arteriosclerosis, the arteries on the right being slightly narrower. Medical examination revealed arterial hypertension, the systolic pressure being 190 mm. of mercury and the diastolic 120 mm. No pathologic changes were found in roentgenograms of the neck, the cervical portion of the spine, the mediastinum or the apexes of the lungs which could account for the Horner syndrome on the right.

The sweating test (fig. 1 *D*) showed well demarcated hypohidrosis of the medial parts of the forehead and the anteroparietal region on the right (the patient was partially bald). Some diminution of sweating also occurred over the lateral part of the right side of the forehead and over the upper right half of the nose.

These findings indicate severe paresis of the sympathetic oculopupillary fibers and sudomotor fibers for the ophthalmic branch of the right trigeminus nerve. Since, however, objective signs of involvement of the fifth nerve were absent and the pain was characteristic of migraine rather than of trigeminal neuralgia, the following diagnosis was made: lesion of the sympathetic plexus caroticus internus or the plexus cavernosus, probably due to hypertensive change of the right internal carotid artery of arteriosclerotic origin (aneurysm?).

A case was observed in which the diagnosis of lesion in the region of the middle cervical ganglion was made.

CASE 5.—H. S., received a stab wound in the left supraclavicular fossa. Partial paralysis of the left deltoid, supraspinatus and infraspinatus muscles and some weakness of the left biceps muscle supervened. Slight hypesthesia of the fourth cervical dermatome was present, possibly owing to an injury of the supraclavicular nerves. A complete Horner syndrome was noted on the left.

Fig. 2 (case 5).—Injury to the cervical portion of the sympathetic chain at the level of the middle cervical ganglion on the left.

The sweating test (fig. 2) revealed complete anhidrosis of the left side of the face, neck and shoulder, including the fifth cervical segment.

Although the pathologic lesion in this case was not verified, the site of the injury and the extent of the area of anhidrosis suggest that the lesion involved the sympathetic chain at the level of the middle cervical ganglion. There is, however, another possible explanation, namely, that the ascending chain was severed above the middle cervical ganglion and the gray rami for the fourth and fifth cervical nerves were divided. The other neurologic findings in this case (lesion of the upper primary fascicle of the brachial plexus) favor the latter interpretation.

SYMPATHETIC INNERVATION OF THE UPPER EXTREMITIES

The preganglionic fibers for the upper extremity originate in the cells of the intermediolateral column from the fourth to the seventh dorsal segment (according to Thomas [8] and Foerster [9]) or to the ninth dorsal segment (Kuntz,[10] Braeucker [11] and Gask and Ross [12]). The preganglionic fibers may ascend within the sympathetic trunk to the inferior cervical ganglion or terminate in the first and second (occasionally also in the third) dorsal ganglia.

The postganglionic fibers of the inferior cervical ganglion, if it exists as a separate structure, supply from the fifth to the eighth cervical segments (Hovelacque [7]). The postganglionic fibers of the first thoracic ganglion innervate the seventh and eighth cervical and the first thoracic segments. Furthermore, the first thoracic ganglion sends deep rami through the vertebral plexus to all cervical nerves as high as the fourth cervical nerve (Hovelacque [7]). The second thoracic ganglion frequently gives off a gray ramus to the first intercostal nerve (Kuntz [10]). Braeucker [11a] found that sweating of the hand was abolished after block of the seventh and eighth cervical and the first dorsal communicant rami with procaine hydrochloride. If the entire upper extremity is to be sympathectomized, the second, and even the third, dorsal ganglion must also be disconnected.[13] In the ordinary cervicothoracic sympathectomy, therefore, the inferior cervical and the first and second dorsal ganglia and occasionally also a ramus arising from the third dorsal ganglion are resected. This produces loss of sympathetic function over the entire upper extremity. In addition, there is deefferentation for the head and neck, because the ascending preganglionic fibers for the middle and superior cervical ganglia are also interrupted by this operation. This is demonstrated by the sweating test in the following cases.

CASE 6.—L. A., had bilateral cervicothoracic sympathectomy for relief from Raynaud's disease of both hands. The inferior cervical and the first thoracic ganglion, which were fused, and the second thoracic ganglion were removed bilaterally. The sweating test (fig. 3 *A*) demonstrated that there was complete

8. Thomas, A.: Les moyens d'exploration du système sympathique et leur valeur, Rev. neurol. **1**:767-928, 1926.

9. Foerster, O.: Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, pp. 1-403.

10. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

11. Braeucker, W.: (*a*) Die Innervation der Schweissdrüsen und die chirurgische Behandlung der Hyperhydrosis, Arch. f. klin. Chir. **149**:718-755, 1928; (*b*) Die Behandlung der Raynaudschen Krankheit, ibid. **167**:807-824, 1931.

12. Gask, G. E., and Ross, J. P.: Surgery of the Sympathetic Nervous System, Baltimore, William Wood & Company, 1934.

13. This extensive resection is necessary in order to denervate the axilla.

anhidrosis of the head, neck, upper extremities and upper part of the chest down to the third rib. Abundant perspiration, however, occurred in both axillary grooves.

CASE 7.—F. P., who suffered from Raynaud's disease of both hands, had had the second and third thoracic ganglia removed (at another clinic). The sweating test showed that on the right side sweating over the head, neck and upper extremity was still retained, though markedly diminished, whereas on the left side there were minimal sweating of the head and neck and a trifle more over the upper

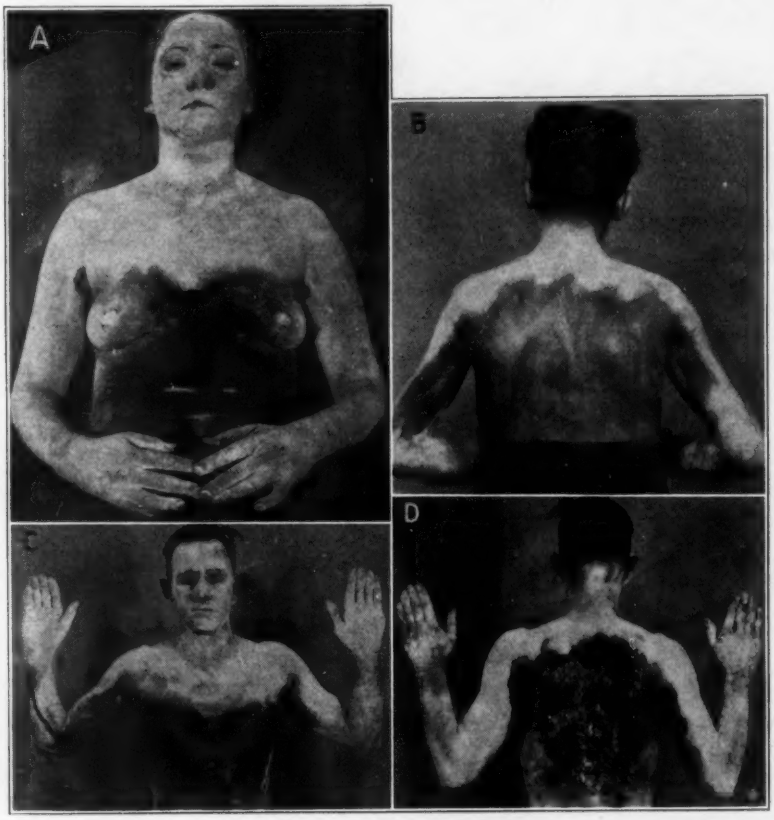

Fig. 3.—*A* (case 6), bilateral resection of the inferior cervical and first and second thoracic sympathetic ganglia. Note sweating of the axillas. *B* (case 8), bilateral resection of the inferior cervical and first and second thoracic sympathetic ganglia. Note sweating in the second thoracic dermatomes. *C* and *D* (case 9), resection of the inferior cervical and first thoracic sympathetic ganglia on the right and of the inferior cervical and first and second thoracic sympathetic ganglia on the left.

extremity. The object of the operation was not accomplished in this case, since only incomplete sympathetic denervation was obtained. At a second operation in this clinic, the first dorsal and the inferior cervical ganglion were resected bilaterally. After the second operation the patient showed complete anhidrosis

of the head, neck, upper extremities and upper part of the chest. The axillary grooves remained dry, in contrast to the results in case 6, in which there was sweating in the axillary areas. This difference is readily explained by the fact that in case 7 the third thoracic ganglia and their rami had also been resected.

We recently had the opportunity to examine a patient who had had bilateral cervicothoracic sympathectomy three years before. In this case the zone of complete anhidrosis was smaller than usual, probably because the subsidiary innervation from the remaining upper part of the thoracic chain had accomplished a certain amount of restitution of function.

CASE 8.—M. L., three years previously had had resection of the inferior cervical and the first and second thoracic ganglia bilaterally for relief from scleroderma of both hands. The sweating test (fig. *3 B*) showed anhidrosis down to the second ribs. Most of the upper extremities remained dry, but marked sweating occurred in the axillas and over the posterointernal aspect of the upper portions of both arms (more extensively on the left). The remaining segmental supply for the third dorsal dermatome, which usually covers only the axillary groove, spread considerably into the denervated second thoracic dermatome.

In another case the surgeon believed he had excised both stellate ganglia; the sweating test revealed, however, that only on the right side had the operation been confined to the stellate ganglion, whereas on the left the second thoracic ganglion must also have been removed.

CASE 9.—F. N., had had cervicodorsal sympathectomy, supposedly stellate ganglionectomy, bilaterally for relief from retinitis pigmentosa. The sweating test (fig. 3 *C* and *D*) showed anhidrosis of the head, neck and upper part of the chest (to the third rib) bilaterally. There were abundant perspiration in the left axilla and some sweating on the inner aspect of the proximal part of the left arm. All other parts of the left upper extremity remained dry. On the right side, not only the axilla and the inner aspect of the upper part of the arm perspired profusely but the ulnar border of the forearm and hand and the dorsum of the third, fourth and fifth fingers showed noticeable sweating.

This result suggests that on the left side sweat fibers destined for the second thoracic dermatome must have been sectioned. On the right side, however, the sympathetic supply for the second thoracic segment was intact and was partially preserved in the first thoracic, and perhaps even the eighth cervical, segment.

It may be mentioned that in all cases of cervicothoracic sympathectomy the borderline between the anhidrotic and the sweating area of the thorax is sharp.

Removal of the sympathetic chain above the inferior cervical ganglion or of the inferior cervical plus the first thoracic ganglion produces not only anhidrosis but a definite Horner syndrome. The oculopupillary fibers pass chiefly through the first dorsal anterior root; they may also be carried by the eighth cervical root, when the plexus is of the prefixed type, and by the second thoracic root, when the plexus is postfixed

(Foerster, Gagel and Mahoney [14]). Hence, a definite Horner syndrome will result if the lesion is limited to the eighth cervical and first dorsal anterior roots or to their white (preganglionic) rami. Loss of sweating over the head or neck, however, may be incomplete in such a case, since the majority of sweat fibers come from below from the second to the fourth anterior dorsal root. If the gray rami (postganglionic fibers) for the eighth cervical and first dorsal roots are involved also, as is usually the case in surgical lesions of this region, more or less sharply defined anhidrosis may be expected over the ulnar side of the hand and forearm. The description of an injury to the brachial plexus will illustrate a dissociated syndrome of this type.

Case 10.—N. S., aged 5 years, had fractured the right humerus eleven months before. After manipulation of the arm paralysis of the hand occurred. Examination showed complete paralysis of all muscles supplied by the radial nerve except the triceps and brachioradialis muscles; in addition, the long flexor muscle of the thumb and the long flexor muscles of the fingers (particularly on the radial side) showed marked weakness. Slight weakness of the flexor carpi radialis, the palmaris longus and the first, second and third interossei muscles was also noted Sensory examination was unsatisfactory. A complete Horner syndrome was present on the right. The sweating test revealed, however, that perspiration was normal and equally distributed over the two sides of the face and neck. There was distinct anhidrosis over the radial side of the right hand and forearm on both the dorsal and the volar surface.

In this case it must be assumed that somatic motor fibers originating in the seventh and eighth cervical and, to a lesser extent, in the first dorsal segments had been damaged. The presence of a Horner syndrome without loss of sweating over the head suggests that the preganglionic sympathetic fibers for the eighth cervical and first thoracic nerves (oculopupillary fibers) had been injured. The loss of sweating over the radial side of the hand and forearm was of a segmental rather than of a peripheral nerve type. This proves that the lesion involved the postganglionic sympathetic fibers mainly for the seventh, and perhaps also for the eighth, cervical dermatome. Obviously, this injury had damaged the somatic motor fibers at the level of, or even distal to, the plexus. On the other hand, there must have been some injury of the eighth cervical and first thoracic roots proximal to their junction with the communicant gray rami.

Lesions involving the first seven cervical nerves proximal to the junction with their communicant gray rami show no disturbance of heat sweating because they do not contain preganglionic sympathetic

14. Foerster, O.; Gagel, O., and Mahoney, W.: Ueber die Anatomie, Physiologie und Pathologie der Pupillarinnervation, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **48**:386-398, 1936.

fibers. If, however, the first seven cervical nerves are sectioned distal to the entrance of the gray rami (postganglionic fibers) complete anhidrosis results.

Any lesion of the sympathetic chain below the first dorsal ganglion causes anhidrosis or marked hypohidrosis over the head and neck, but fails to produce a Horner syndrome because the oculopupillary fibers are intact. This is demonstrated in case 7, in which, after resection of the second and third dorsal ganglia, marked diminution of sweating but no Horner syndrome occurred.

SYMPATHETIC INNERVATION OF THE TRUNK

The sympathetic supply for the skin of the trunk is less complicated than that for the head and the upper extremity. Here, the primitive strictly segmental distribution can readily be recognized. It is believed that the sympathetic supply for the thoracic segments originates in the cells of the intermediolateral column from the fifth to the twelfth dorsal segment (Thomas [8]), and probably over a wider area of the cord. The preganglionic fibers of one middorsal anterior root are widely distributed through the chain, in which they ascend and descend for considerable distances. Thus, after intradural section of the fifth anterior thoracic root, Foerster stimulated the peripheral end with a faradic current and produced sweating from the axilla to the level of the umbilicus; i. e., the perspiring area supplied by preganglionic fibers of one motor nerve root corresponds to an area of five or six sensory dermatomes (Guttmann and List [2a]). The diffuse distribution of sympathetic fibers in the thoracic chain explains the fact that resection of one or two anterior roots or mere interruption of the interganglionate portion of the trunk is followed by no loss of sweating. Each thoracic ganglion apparently receives preganglionic fibers of from four to six anterior roots.

The situation changes, however, in the case of lesions of the postganglionic fibers. Destruction of a single thoracic sympathetic ganglion produces no loss of sweating, since the cutaneous area supplied by one thoracic ganglion is overlapped by those supplied by the adjacent ganglia above and below. However, as soon as all the postganglionic fibers (gray rami) of at least two ganglia are severed, a clearcut zone of anhidrosis is usually demonstrable. As every gray ramus carries the segmental supply for its corresponding intercostal nerve, the area of anhidrosis forms a segmental band closely resembling the distribution of that intercostal nerve. These facts are well demonstrated in cases of low thoracic sympathectomy (resection of the splanchnic nerves for relief from high blood pressure). This operation, devised by one of us (M. M. P.), consists in resection of the major and minor splanchnic nerves and of the tenth and eleventh, and usually of the twelfth, dorsal

sympathetic ganglia with their rami. In some cases it is necessary to sacrifice the eleventh intercostal nerve.

CASE 11.—F. R., had low dorsal sympathectomy and section of the splanchnic nerves for relief from malignant arterial hypertension. The eleventh intercostal nerve was saved on both sides. The sweating tet (fig. 4 *A*) showed a sharply limited band of complete anhidrosis over the tenth and eleventh dorsal segments.

CASE 12.—A. B., had resection of the tenth, eleventh and twelfth dorsal sympathetic ganglia and the greater and lesser splanchnic nerves bilaterally for relief from arterial hypertension. The eleventh intercostal nerve on the right side was sectioned. The sweating test revealed anhidrosis over the eleventh dorsal segment bilaterally. Above this level there was marked perilesionary hyperhidrosis, from

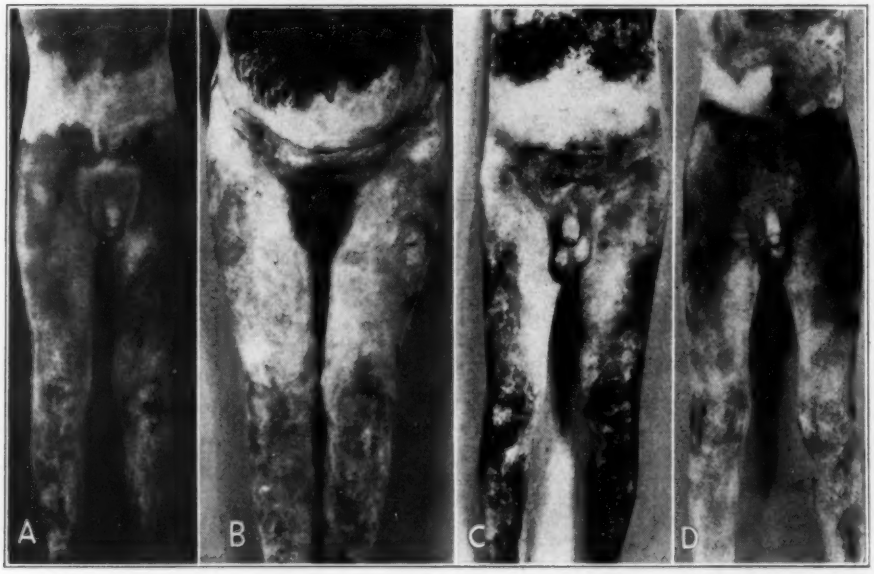

Fig 4.—*A* (case 11), bilateral resection of the tenth and eleventh thoracic sympathetic ganglia; *B* (case 13) bilateral resection of the tenth, eleventh and twelfth thoracic sympathetic ganglia; *C* (case 14), bilateral resection of the tenth, eleventh and twelfth thoracic sympathetic ganglia, and *D* (case 15), bilateral (?) resection of the tenth and eleventh thoracic sympathetic ganglia.

the eighth to the tenth dorsal segment on the right. Sweating over the twelfth dorsal and first lumbar segments perhaps was slightly diminished on both sides.

These two observations prove that section of the eleventh intercostal nerve is not responsible for the band of anhidrosis over the corresponding segment. Even after removal of three ganglia, the tenth, eleventh and twelfth dorsal ganglia, the supply of the intact neighboring ganglia may overlap so much that the area of complete anhidrosis is reduced to a narrow band in the eleventh dorsal dermatome. The slight diminution of sweating over the twelfth dorsal and the first lumbar segment

suggests that a number of descending fibers for the lumbar portion of the chain must also have been interrupted. This is even better demonstrated in the following case.

CASE 13.—E. M., had low dorsal sympathectomy, from the tenth to the twelfth dorsal ganglion and resection of the splanchnic nerves bilaterally for relief from arterial hypertension. Heat sweating (fig. 4*B*) was entirely abolished over the tenth and eleventh dorsal segments and markedly reduced over the twelfth dorsal and the first and second lumbar segments on both sides. Here, most of the descending (preganglionic?) fibers for the thighs apparently originated in the three lowest dorsal ganglia.

In contrast to the findings in cases 12 and 13, the following observation suggests interruption of fibers ascending in the chain.

CASE 14.—J. M., had sympathectomy, from the tenth to the twelfth dorsal ganglion, and resection of the splanchnic nerves bilaterally for relief from arterial hypertension. The eleventh intercostal nerves were also resected. The sweating test (fig. 4*C*) produced an unusually wide belt of anhidrosis, from the ninth to the eleventh dorsal segments. In this case ascending fibers for the ninth dorsal and higher ganglia must have been interrupted, or perhaps rami from the ninth ganglion were injured.

When resection of the sympathetic chain is not extensive enough little loss of sweating may occur, because the auxiliary supply of the intact neighboring ganglia overcomes the defect.

CASE 15.—H. v. d. B., had low dorsal sympathectomy and resection of the splanchnic nerves bilaterally for relief from high blood pressure. Here, apparently only the tenth and eleventh dorsal ganglia were removed; in addition, the right eleventh intercostal nerve was sectioned. The sweating test (fig. 4*D*) revealed that on the right side a sharply defined zone of anhidrosis occurred in the tenth, and extended slightly into the eleventh, dorsal segment. On the left side there was only a narrow strip of moderate hypohidrosis in the eleventh dorsal segment. Pronounced perilesionary hyperhidrosis was seen bilaterally in the twelfth dorsal and, to a lesser degree, in the first and second lumbar segments.

The following case was particularly interesting for study of the "remaining perspiration" of the trunk.

CASE 16.—H. W., suffered from Raynaud's disease and arterial hypertension; hence, cervicothoracic, low thoracic and lumbar sympathectomies (with resection of the splanchnic nerves) were performed bilaterally. After removal of the inferior cervical, the first, second, tenth and eleventh dorsal and the second, third and fourth lumbar ganglia, the preserved ganglia, from the third to the ninth dorsal, maintained thermoregulatory sweating over the cutaneous area of from the third to the tenth dorsal segment, inclusive (fig. 5).

SYMPATHETIC INNERVATION OF THE LOWER EXTREMITIES

The cutaneous sympathetic supply for the legs originates in cells of the intermediolateral column of from the tenth dorsal to the third lumbar segment. The preganglionic fibers travel through from the tenth dorsal

to the third lumbar anterior root, most of them passing caudad within the lumbar and sacral portions of the chain. The postganglionic fibers join the lumbrosacral plexus segmentally as gray rami. The typical lumbar sympathectomy consists in resection of the second, third and fourth lumbar ganglia; hence, this operation accomplishes postganglionic denervation of from the second to the fourth lumbar segments, but preganglionic denervation of the fifth lumbar and all the sacral segments.

Fig. 5 (case 16).—Bilateral resection of the following: the inferior cervical; the first, second, tenth and eleventh thoracic, and the second, third and fourth lumbar sympathetic ganglia.

After lumbar sympathectomy anhidrosis over all dermatomes below the first lumbar should be expected, but ordinarily some sweating is retained over the second lumbar dermatome on account of the segmental overlap from above. The results of this operation are illustrated in 3 cases.

CASE 17.—In the case of H. S., lumbar sympathectomy (from the second to the fourth lumbar ganglion) had been performed bilaterally for treatment of

megacolon. The sweating test (fig. 6 *A* and *B*) showed absence of perspiration over the lower portions of the legs and feet. Posteriorly the buttocks and thighs (sacral segments) remained dry, but anteriorly slight sweating occurred within the second lumbar dermatomes. There was striking perilesionary hyperhidrosis in the area supplied by the first lumbar segment, defining the upper boundary of the lesion.

CASE 18.—W. H., had been subjected to left lumbar sympathectomy for treatment of megacolon. Anhidrosis was present over the entire left lower extremity, but a band of increased perspiration delineated the lower border of the first lumbar segment on the posterolateral aspect of the leg (fig. 6 *C* and *D*). Absence of a definite borderline on the anterior aspect of the thigh was due to the fact that on both sides little sweating had occurred over the groins and lower part of the abdomen. However, persistence of sweating over the lumbar region of the back bilaterally proved that the function of the low thoracic sympathetic ganglia was not impaired. Furthermore, the level of sweating was checked by measurements of cutaneous temperatures, which became elevated in the upper part of the second lumbar segment on the left.

CASE 7.—F. P., who suffered from Raynaud's disease of the hands and feet, had had lumbar sympathectomy at another clinic. The patient was examined one year after operation. There were complete anhidrosis below and diminished sweating over the fourth lumbar segment. It cannot be decided whether these findings were due to functional restitution or whether at operation the second and third lumbar ganglia were left intact.

The sympathetic innervation of the legs could be studied also by experiments with stimulation in the course of operations.

CASE 16 (H. W.).—The right sympathetic chain was picked up about the level of the third lumbar ganglion. Without any of the connections being severed, the trunk was stimulated with a faradic current for one minute. Marked sweating occurred over the right foot, more on the dorsal than on the plantar surface, and some perspiration appeared over the right calf, up to the knee.

CASE 19.—In the case of L. R., who had Raynaud's disease of the feet and hypertension, the sympathetic chain was severed below the fourth lumbar ganglion, and the peripheral end was stimulated with a faradic current. Marked sweating of the sole was observed, while the calf remained dry (fig. 7). Scarcely any perspiration formed on the dorsum of the foot.

The following 2 patients suffering from arterial hypertension associated with Raynaud's syndrome underwent combined low thoracic sympathectomy, resection of the splanchnic nerves and lumbar sympathectomy.

CASE 19 (L. R.).—The extent of the sympathectomy was verified at autopsy. On the right side the sympathetic chain from the tenth dorsal to the fourth lumbar ganglion, inclusive, had been removed. On the left side, however, the lower half of the twelfth dorsal ganglion, which consisted of two divisions, and the first lumbar ganglion were left intact, while the tenth, eleventh and upper half of the twelfth dorsal ganglion and the second, third and fourth lumbar ganglia had been resected. A previous sweating test had demonstrated anhidrosis over the right side, from the tenth dorsal segment down. On the left side a slight degree of perspiration occurred over the twelfth dorsal and the first lumbar segment.

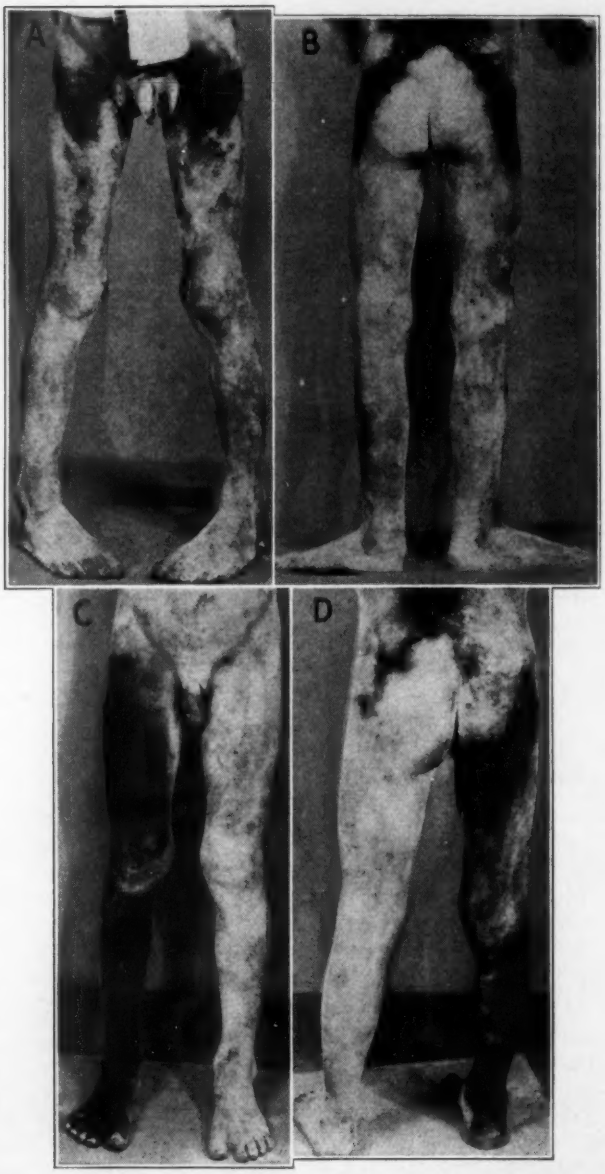

Fig. 6.—*A* and *B* (case 17), bilateral resection of the second, third and fourth lumbar sympathetic ganglia, showing the "perilesionary" hyperhidrosis in the first lumbar dermatomes, and (case 18), and *D* resection of the second. third and fourth lumbar sympathetic ganglia on the left.

CASE 16 (H. W.).—The tenth and the eleventh dorsal and the second, third and fourth lumbar ganglia were removed on both sides. The sweating test (fig. 5) revealed only slight "remaining perspiration" over the twelfth dorsal and first lumbar dermatomes on the right. On the left side sweating was more pronounced, covering the twelfth dorsal and the first and second lumbar segments. Preservation of sweating over the left second lumbar segment suggests either that the second lumbar ganglion was not completely removed or that accessory postganglionic fibers from the first lumbar segment supplied the second lumbar dermatome.

Case 16 is of special interest, for after three operations the patient probably has a more reduced sympathetic system than any other human being in the world. Only from the third to the ninth dorsal ganglion and the twelfth dorsal and first lumbar ganglia remained intact, whereas the first and second dorsal ganglia with the total cervical outflow and the tenth and eleventh dorsal and second, third and fourth lumbar ganglia with the total sacral outflow were removed. In addition, the visceral fibers in the major and minor splanchnic nerves were resected. Although

Fig. 7 (case 19).—Faradic stimulation of the lumbar portion of the sympathetic chain below the fourth lumbar ganglion on the right.

heat sweating was limited to a relatively small area of the surface, no difficulties in thermoregulation developed in the patient, who, being a farmer, is exposed to high outside temperatures.

SUMMARY

Localized lesions of the sympathetic chain and of its rami lead to circumscribed loss of thermoregulatory sweating. The area of anhidrosis is frequently bounded by a zone of increased perspiration (so-called perilesionary hyperhidrosis).

The typical areas of anhidrosis which occur after various forms of sympathectomy are described.

The postganglionic sweat fibers contained in the gray communicant rami supply the skin in a segmental manner corresponding to the sensory radicular innervation.

The thermoregulatory sweating test is a simple and accurate clinical method to determine the extent and site of lesions in the sympathetic nervous system.

VESICAL ABNORMALITIES ASSOCIATED WITH THE PARKINSONIAN SYNDROME

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BALTIMORE

It has been my plan to study disturbances of micturition after injury of different anatomic structures in the central nervous system. The present report deals with extrapyramidal influences from the region of the forebrain. The experimental side of the problem was approached by section of the tegmentum of the midbrain, the cerebral peduncles being left intact. This operation produced changes in the vesical function of cats, which have been described (Levin and Langworthy [1]). Clinically, patients with the parkinsonian syndrome were chosen to show abnormalities of micturition produced by injury of the basal ganglia or their projection fibers. From the anatomic point of view the observations were unsatisfactory, as the lesions were not circumscribed.

There are frequent references, particularly in the German literature, to disturbances of micturition associated with disease of the corpus striatum or with the parkinsonian syndrome (Czylharz and Marburg [2]). Unfortunately, these papers give little specific information. Adler [3] presented a diagram of his conception of the control of micturition by the brain, showing reflex pathways through the corpus striatum. Bechterew and Mislowsky [4] and Bechterew and Meyer [5] expressed the belief that the increased tone of the bladder muscle is associated with lesion of the basal ganglia. Lichtenstern and Marburg [6] found hypertonicity of the external sphincter muscle with retention of urine associ-

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From the Subdepartment of Neurology, the Johns Hopkins University.

1. Levin, P. M., and Langworthy, O. R.: Extrapyramidal Control of Micturition: The Effects of Lesions of the Tegmentum of the Mid-Brain, Am. J. Physiol. **118**:483, 1937.

2. Czylharz, E., and Marburg, O.: Weitere Bemerkungen zur Frage der cerebralen Blasenstörungen, Wien. klin. Wchnschr. **15**:788, 1902.

3. Adler, A.: Ueber organisch (kortikale) und funktionell nervöse Blasenstörungen, Deutsche Ztschr. f. Nervenh. **65**:72, 1920.

4. Bechterew, W., and Mislowsky: Die Hirncentra für die Bewegung der Harnblase, Neurol. Centralbl. **7**:505, 1888.

5. Meyer, S.: Ueber die Rindencentra Sphincteris ani et vesicae, Neurol. Centralbl. **12**:81, 1893.

6. Lichtenstern, R., and Marburg, O.: Ueber initiale Blasenstörungen bei organischen Nervenkrankheiten, Ztschr. f. urol. Chir. **38**:145, 1933.

ated with injury of the globus pallidus. Minkowski [7] concluded that injury to the corpus striatum occasionally gives rise to tonic incontinence. Schwarz [8] found dysuria associated with lesions of the corpus striatum. Caulk and Greditzer [9] mentioned relaxation of the vesical sphincters in cases of paralysis agitans.

Lendrum and Moersch [10] studied 250 patients with disturbances of micturition dependent on faulty innervation of the bladder. Four of this group showed the parkinsonian syndrome.

Graphic records of vesical activity have been made from a considerable number of patients with injuries of the central nervous system. The graphs demonstrated characteristic changes associated with damage to certain specific groups of cells and fibers (Langworthy, Lewis, Dees and Hesser [11]). Thus, patients with bilateral involvement of the corticospinal tract complained of urgency, frequency and incontinence. The volume of the bladder was small and the contraction of the vesical muscle of unusual force. The stretch reflex was hyperactive. The classification has an anatomic basis. The abnormalities associated with injury to the corticospinal tracts are identical whatever the etiologic agent.

A number of patients with the parkinsonian syndrome have been known to show abnormalities in function of glands and smooth muscle, as well as of striated muscle. These difficulties do not occur even in the majority of patients, but they are usually marked when present. There is oversecretion of glands, manifested as increased salivation, sweating, greasiness of the face and, in 1 patient who was seen recently, excessive lacrimation. Vague complaints of fulness and pain in the abdomen after meals suggest involvement of the smooth muscle of the gastrointestinal tract.

Micturition was studied in patients with the typical changes in striated muscle characteristic of the parkinsonian syndrome whether or not they complained of disturbances in vesical function. It is obvious that the greatest change in the vesical record would be expected

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7. Minkowski, M.: Ueber cerebrale Blasenstörungen, Deutsche Ztschr. f. Nervenh. **33**:127, 1907.

8. Schwarz, O.: Die nervöse Versorgung der Harnblase, in von Lichtenberg, A.; Voeleker, F., and Wildbolz, H.: Handbuch der Urologie, Berlin, Julius Springer, 1926, vol. 1, p. 426.

9. Caulk, J. R., and Greditzer, H. G.: Observations on the Bladder in Diseases of the Central Nervous System: An Analytical Study of One Hundred and Seventeen Cases, Am. J. Syph. **1**:42, 1917.

10. Lendrum, F. C., and Moersch, F. P.: Neurologic Diagnosis in Two Hundred and Fifty Cases of Cord Bladder, J. A. M. A. **102**:658 (March 3) 1934.

11. Lewis, L. G.; Dees, L. E., and Hesser, F. H.: A Clinical Study of the Control of the Bladder by the Central Nervous System, Bull. Johns Hopkins Hosp. **58**:89, 1936.

in patients who had noticed symptoms referable to the bladder. Chronic encephalitis and the vascular changes in the brain responsible for the senile parkinsonian syndrome cause widespread damage in the diencephalon and midbrain, injuring particularly the so-called basal ganglia and their connections. The symptoms of the parkinsonian syndrome itself vary in that either tremor or rigidity of the striated muscles may predominate. Other accessory symptoms may appear, owing to injury of adjacent structures.

STATISTICAL STUDY OF VESICAL COMPLAINTS IN PATIENTS WITH THE PARKINSONIAN SYNDROME

Certain patients with the parkinsonian syndrome complain of frequency of micturition. When this is a symptom it causes considerable distress. Histories from the outpatient department were not ideal for statistical work, as the urinary abnormalities were not stressed in obtaining answers to the usual questions. Of 130 patients with chronic encephalitis, 14 complained of frequency of micturation, and 2, of urgency. Eleven had nocturia, so that they had to micturate three or four times during the night. As most of the patients were young adults, the nocturia is significant from a neurologic standpoint. Frequency was dissociated from urgency of micturition. None of the patients with disturbances of the bladder showed clinical evidence of injury to the corticospinal fibers.

Another group of histories of 81 patients with parkinsonian disease of arteriosclerotic origin or paralysis agitans were examined. Fifteen of these complained of frequency of micturition, and 18 had to micturate from two to six times during the night. Nocturia in the older patients is not significant. Only 3 of those who complained of frequency were aware of urgency of micturition.

METHOD AND NORMAL RECORDS USED AS CONTROLS

The methods of making the graphic records need not be discussed, since they have been described in previous papers (Lewis, Langworthy and Dees [12]). We used an air and water manometer, which recorded small changes in intravesical pressure.

Experiments with vesical activity after injuries to the nervous system required that records be taken as controls from normal persons with no local disease of the urinary tract or neurologic signs. A number of these records were made, one of which is shown in figure 1. The vesical volume was 500 cc. of water. The resting pressure in the empty bladder was 1 cm. and remained below 7 cm. until filling was complete. The vertical lines on the graph spaced at fairly regular intervals indicate the points at which 50 cc. of fluid was introduced into the

12. Lewis, L. G.; Langworthy, O. R., and Dees, J. E.: Bladder Abnormalities Due to Injury of Motor Pathways in the Nervous System, J. A. M. A. **105**:2126 (Dec. 28) 1935.

system. After the introduction of these units of fluid the intravesical pressure fell quickly to a resting level. This resting pressure was well maintained, and no waves of vesical contraction occurred during filling. When 500 cc. had entered the bladder, a strong, sustained contraction of the detrusor muscle raised the pressure to 54 cm. of water, and fluid escaped from the urethra around the catheter. A notch in the record of the contraction wave indicates a momentary effort on the part of the patient to control the contraction.

GRAPHIC VESICAL RECORDS IN PARKINSONIAN DISEASE

Records were also obtained from 17 persons who showed the parkinsonian syndrome. Fifteen of these demonstrated abnormalities of vesical function. The case histories of 7 are reported in detail.

CASE 1.—A. S., a white man aged 48, married, was admitted to the hospital with a unilateral parkinsonian syndrome and complaints centering around the genitourinary system. There was "dripping from the penis." The urinary symp-

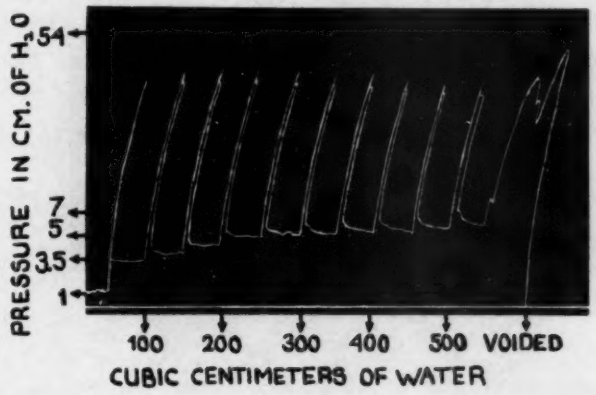

Fig. 1.—Record of normal vesical filling. The vertical lines spaced at fairly equal intervals indicate the points at which 50 cc. increments of fluid were introduced into the system.

toms appeared to be entirely on a neurologic basis. The family and past history were unimportant. There was no history of an attack of acute lethargic encephalitis.

One year before the patient noticed a urethral discharge of clear fluid, which was enough only to dampen the clothes. There was slight dribbling after micturition. He had nocturia two or three times and voided five or six times during the day. For three months he had been unable to obtain an erection, although libido was normal. Just preceding this period emission had been premature.

For less than a year he had noticed tremulousness and slowness of writing. The right hand was stiff and tired, and the right arm did not swing in walking. When he played the mechanical games in glass boxes found in amusement parks, he could not manipulate the handles correctly. Walking became difficult because the right foot dragged. For two or three months the toes on the right foot had turned under the foot in contraction.

On examination it was found that the patient walked well, but did not swing the right arm. The right side of the face was immobile. The right palpebral fissure was wider than the left. The right pupil was larger than the left.

The retinal arteries showed moderate sclerosis. There was a rhythmic tremor of the eyelids. The tongue protruded to the right.

Tone was definitely increased in the muscles of the right arm and leg. Cogwheel rigidity could be demonstrated at the right elbow and wrist. Finer movements of the right hand were clumsy, and writing tended to show a progressive decrease in size. The right foot was colder than the left.

Although the deep reflexes were hyperactive there was little difference on the two sides. The abdominal and cremasteric reflexes were active. There was no Babinski reflex. No abnormalities of sensation were present.

Careful urologic examination as a routine failed to show further abnormalities. The Wassermann reaction of the blood was negative. The blood pressure was 150 systolic and 95 diastolic.

In summary, the patient showed a unilateral parkinsonian syndrome involving the right side of the body, with vesical and sexual disturbances, mild arteriosclerosis and hypertension. It was the impression that the disease was chronic lethargic encephalitis.

Two graphic records of vesical filling *A* and *B* are shown in the order in which they were obtained on the same day, (fig. 2). While they are similar they

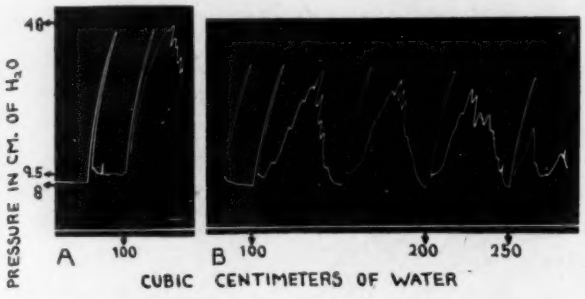

Fig. 2.—Two records made on the same day from a patient with a unilateral parkinsonian syndrome whose complaints were primarily concerned with disturbances of micturition. A description is given in the text.

demonstrate different facts. In the first experiment (*A*) the pressure in the empty bladder was 8 cm. of water. After the addition of 50 cc. the resting pressure was 9.5 cm. When the volume was increased to 100 cc. the pressure rose to 48 cm. and fluid escaped around the catheter.

The second reading (*B*) is similar to the first during the first part of filling. With 100 cc. of water in the bladder, the pressure rose to 43 cm., and the bladder did not empty completely around the catheter. When the volume was increased to 150 cc. the pressure rose to 40 cm., and when it was 200 cc. the pressure was 38 cm. Finally, with 250 cc. of water in the bladder the pressure rose to only 30 cm. The resting pressure in the bladder was then 18 cm., and the patient was distinctly uncomfortable. For this reason, the vesical filling was stopped.

It will be noticed that as filling progressed the contraction of the vesical muscle became progressively less strong. This may be dependent on either of two factors. The muscular contractions may have shown a tendency to tire. The other possibility takes into consideration the strength of the sensory impulse. As the volume of the bladder was progressively increased, the addition of a unit quantity of fluid caused less marked stretching of the vesical wall. It should also be observed that the waves of contraction started only at a definite interval

after the introduction of fluid. The stretch responses were not as active as after injury of the efferent pathways from the cerebral cortex (Lewis, Langworthy and Dees [12]).

CASE 2.—A white man aged 56 had noticed tremor of the right arm eleven years before. Three years later the tremor spread to the left arm and to the legs. There were slowness and difficulty of voluntary activity. Examination revealed expressionless facies and stooped posture. The speech was low, slow and monotonous. A coarse, regular tremor was present in the arms and, to a less extent, in the legs. All movements were of small amplitude. Cogwheel rigidity could be demonstrated in the extremities. There were loss of associated movements in walking and some tendency to festination. The patient occasionally fell backward. The deep reflexes were normally active. There was no Hoffmann or Babinski reflex. The patient noticed frequency of micturition. He had to empty the bladder every two hours during the day and three or four times at night.

The external sphincter muscle was resistant to the passage of a catheter. Figure 3 shows the record of vesical filling. The pressure in the empty bladder

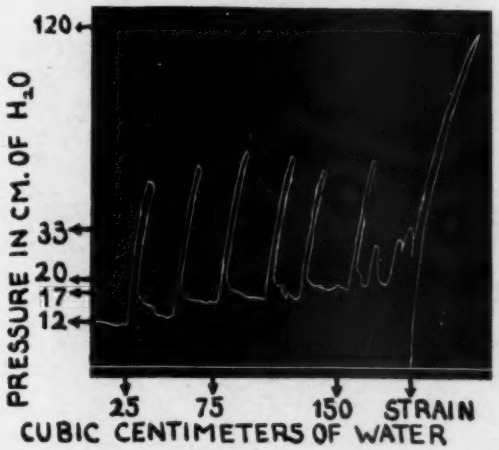

Fig. 3.—Graphic record of vesical filling from a patient with the parkinsonian syndrome. The resting pressure was high in the empty bladder and during filling. The volume of the bladder was small.

was 12 cm. of water. Fluid was introduced in quantities of 25 cc., and the capacity was reached when the bladder held 150 cc. The pressure then rose to 120 cm., and fluid escaped from the urethra. The pressure in the empty bladder was higher than normal. During the period of filling the resting pressure was from 12 to 20 cm. of water. The pressure returned fairly quickly to a resting level after fluid was added. There was no evidence of hyperactivity of the stretch reflex. The only clearcut response to stretch was at the end of filling, when the bladder had reached its capacity. This curve shows two marked deviations from the normal. The resting pressure was high both in the empty bladder and during filling, and the capacity was decreased. The stretch reflex was normally active.

CASE 3.—A Negro aged 43 for nine years had suffered from diminution of ability to perform free movements of the extremities. There was no tremor.

Marked rigidity of the extremities was demonstrable on passive movement. The patient showed a marked tendency to hold any attitude in which he was placed. Salivation was exceedingly profuse. Frequency of micturition or other disturbance of the bladder had not been noticed.

The record in this case appears in figure 4 and is similar to that in figure 3. The resting pressure in the empty bladder was high (7 cm.) and remained so

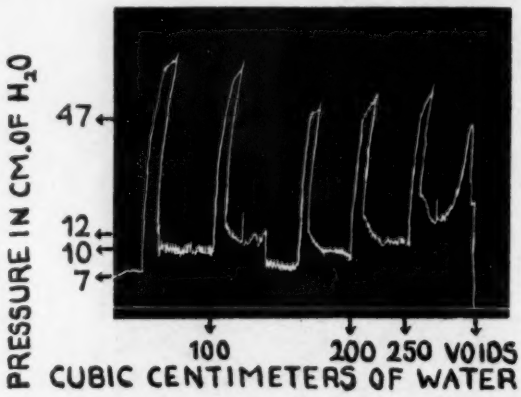

Fig. 4.—A record from another patient with parkinsonian disease, showing findings similar to those seen in figure 2.

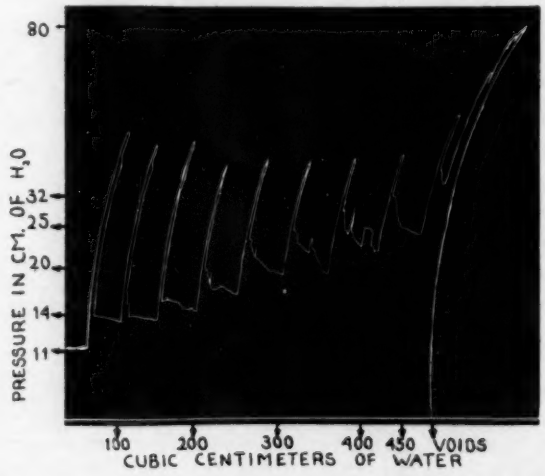

Fig. 5.—Graphic vesical record from a patient with the parkinsonian syndrome, showing an abnormally high intravesical pressure and a normal volume of the bladder.

throughout filling. After a quantity of fluid was added, the pressure fell at once to a resting level. Coughing and other movements caused extraneous changes in the record of resting pressure; these were seen at a capacity of 100 cc. At that of 250 cc. the pressure fell, and the patient coughed. The pressure then rose steadily to 47 cm., and fluid escaped from the urethra.

CASE 4.—In a white man aged 38 the parkinsonian syndrome developed six years after an attack of acute lethargic encephalitis. Rigidity of a cogwheel type involved all the extremities. Tremor was not a marked feature. There were no neurologic findings suggesting injury of the corticospinal tracts or history of urinary disturbances.

The pressure in the empty bladder was 11 cm. and reached 32 cm. before filling was complete (fig. 5). The pressure rose by a series of steps during filling, which indicates that the organ failed to adapt to increasing volumes. The volume was 450 cc., which is within normal limits. Any irregularity of the pressure was due to movement on the part of the patient. When the volume exceeded 250 cc. the pressure fell slowly to a resting level. At 450 cc. the pressure rose to 80 cm., and the bladder emptied. This failure of the bladder to accommodate to increasing volumes of fluid was abnormal. Similar records have been obtained from a contracted bladder after drainage by catheterization.

CASE 5.—A white man aged 37 showed the parkinsonian syndrome after encephalitis. Rigidity was a more prominent feature than tremor. He was unable to walk and was confined to bed. The deep reflexes were normally active; the

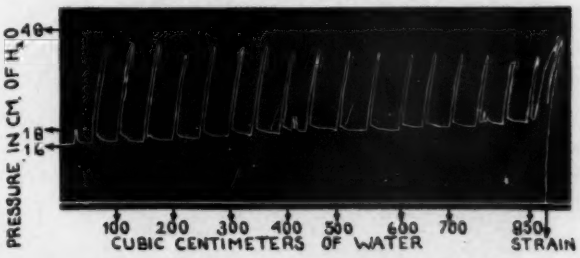

Fig. 6.—Graphic record from a patient with a parkinsonian syndrome in whom the resting intravesical pressure was high and the volume of the bladder greater than the average.

Babinski reflex was not elicited. The patient had noticed slight hesitancy in micturition.

Figure 6 shows high resting pressure both with the bladder empty and during filling. The volume of the bladder was above the average, and the patient felt discomfort only when the capacity was 830 cc. He was then asked to attempt micturition. The pressure increased to only 48 cm., and this rise was not maintained. No fluid escaped from the urethra.

CASE 6.—A man aged 42, a Chinese, had noticed difficulty in voluntary movement for four years. There were tremor of the extremities and cogwheel rigidity. Loss of spontaneous activity was marked. All associated movements were lost. The deep reflexes were normally active, and the Babinski reflex was not elicited. The patient noticed that for periods he had to empty the bladder frequently during the day and three or four times at night.

The resting pressure in the empty bladder was 2 cm., and only 5 cm. when filling was complete (fig. 7). Respiratory waves and movement on the part of the patient, but no true vesical contractions, were recorded during filling. At a volume of 250 cc. a strong contraction raised the pressure to 75 cm., causing the bladder to empty.

CASE 7.—A white man aged 34 showed such extreme hypertonus of the striated muscles that he was almost unable to move. Tremor was slight, but was evidenced in cogwheel rigidity. Retropulsion interfered with walking. Signs of involvement of the corticospinal tracts were not evident. The patient noticed frequency of micturition, as often as every hour.

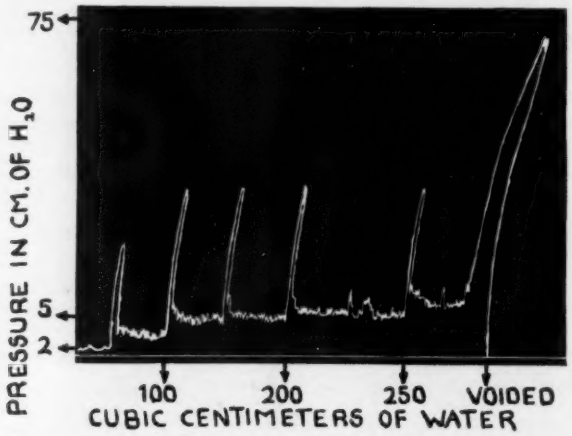

Fig. 7.—Record from a patient with parkinsonian disease with a small volume of the bladder and a normal resting intravesical pressure.

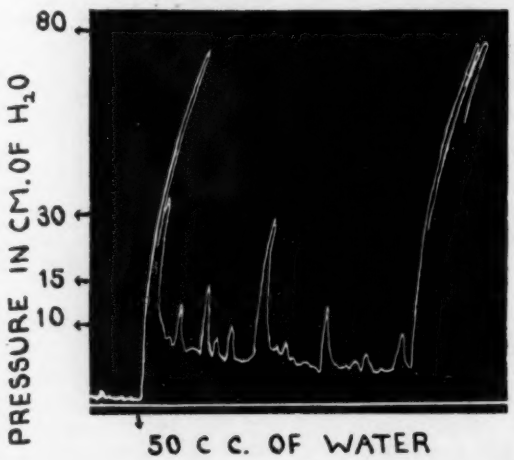

Fig. 8.—Record from a patient with the parkinsonian syndrome the capacity of whose bladder was only 50 cc. The waves of contraction suggest an injury to the tonic reflex arcs in the midbrain.

The resting pressure in the empty bladder was 1 cm. (fig. 8). A stretch reflex followed the introduction of 50 cc. of water, and the pressure fell slowly to a resting level. Then rhythmic waves of vesical contraction, of different amplitudes, appeared. They continued until a sustained contraction raised the pressure to 80 cm. and the bladder emptied.

COMMENT

The records obtained from these patients with the parkinsonian syndrome showed certain abnormalities. The resting intravesical pressure tended to be high, and in general the bladder held a small volume of fluid. In one of the records waves of contraction appeared during filling. In one case the bladder held an unusually large quantity of fluid, although at high pressure. It is proposed to discuss these records in terms of the little that is known concerning the control of the bladder by the central nervous system. The variable extent of the anatomic changes may well account for the different changes seen in the vesical records.

A. High Resting Intravesical Pressure.—In certain of the patients the resting pressure in the bladder was high both with the bladder empty and during filling. The resting pressure in the empty bladder of a normal person is never zero, but it is seldom greater than 2 cm. of water. In contrast, the pressure was 16 cm. in 1 of the patients with the parkinsonian syndrome. The normal person feels a strong desire to micturate before the pressure reaches 10 cm. Before filling was complete the pressure in the bladder of a patient with parkinsonian disease sometimes reached 32 cm. of water.

Two explanations for the unusual height of the intravesical pressure present themselves. It may be dependent on increased intra-abdominal pressure produced by the rigidity of the abdominal wall. Kelling [13] showed that the muscles of the abdominal wall normally make adaptation of their posture to changes in intra-abdominal pressure. It is more probable that the increased pressure is due to the effect of the nerve lesion on the detrusor muscle itself.

Tauber, Lewis and Langworthy [14] studied vesical activity in a group of patients with schizophrenia showing a marked degree of catalepsy. The initial intravesical pressure in the empty bladder was as a rule within normal limits, but the pressure increased rapidly and revealed an unusually high resting level after the addition of fluid.

It is known that bulbocapnine produces a condition in animals which resembles catalepsy. Accordingly, 5 cats were given from 80 to 100 mg. of bulbocapnine, which gave rise to marked catalepsy. In the graphic records of vesical activity the resting intravesical pressure was uniformly high.

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13. Kelling, G.: Untersuchungen über die Spannungszustände der Bauchwand, des Magens, und der Darmwand, Ztschr. f. Biol. **44**:161, 1903.

14. Tauber, E. S.; Lewis, L. G., and Langworthy, O. R.: Vesical Activity in Schizophrenic States Associated with Catalepsy, Arch. Neurol. & Psychiat. **39**: 14 (Jan.) 1938.

Kolb [15] recently studied the effect of the abdominal muscles on intravesical pressure. After making a normal reading during filling of the bladder, he cut the thoracic and lumbar nerves supplying the abdominal muscles. The wall of the bladder became extremely relaxed. At the end of eight weeks there was little change in the resting pressure at which fluid was held in the bladder. Later, he gave the cat bulbocapnine and again made a determination of the resting pressure at different stages of filling. This pressure was higher than normal and approximated that found in normal cats under the influence of bulbocapnine. These experiments suggest that bulbocapnine raises the intravesical pressure by its action on the wall of the bladder or the local vesical nerve plexus. They support the hypothesis that the high intravesical pressure in patients with the parkinsonian syndrome is due to a change in tone of the muscle of the bladder rather than of the abdominal wall.

B. Decreased Vesical Capacity.—Certain patients complained of frequency of micturition, and study showed that the capacity of the bladder was decreased well below the normal. This again suggests that hypertonus of the muscle composing the wall of the bladder decreased the lumen. Bilateral injury of the corticospinal tracts is known to decrease the vesical volume (Lewis, Langworthy and Dees [12]); the stretch reflex is hyperactive. The patients in the present series gave no evidence of injury to the corticospinal tracts, nor was the stretch reflex hyperactive.

Two motor pathways from the brain influencing the function of the detrusor muscle are known. The cerebral cortex controls activity of the bladder (Langworthy and Kolb [16]), and bilateral injury of the corticospinal tracts produces characteristic abnormalities (Lewis, Langworthy and Dees [12]). In addition, reflex pathways through the upper portion of the midbrain control tone in the detrusor muscle (Langworthy and Kolb [17]). When this reflex pathway is released from control of the forebrain, the volume of the bladder becomes smaller as the stretch reflex is no longer inhibited. The pathway runs in the lateral columns of the cord, close to the corticospinal fibers. In the patients in the present series the corticospinal tracts were uninjured. It is possible that the reflexes through the midbrain can be released

15. Kolb, L. C., and Langworthy, O. R.: A Comparative Study of the Effects of Barbiturates, Ether and Bulbocapnine on Micturition, J. Pharmacol. & Exper. Therap., July 1938, to be published.

16. Langworthy, O. R., and Kolb, L. C.: Demonstration of Encephalic Control of Micturition by Electrical Stimulation, Bull. Johns Hopkins Hosp. **56**:37, 1935.

17. Langworthy, O. R., and Kolb, L. C.: The Encephalic Control of Tonus in the Urinary Bladder, Brain **56**:371, 1933.

from control of the forebrain without injury to the corticospinal tracts. Certainly, the high resting intravesical pressure and the small capacity of the bladder suggest an increase in tone of the detrusor muscle.

Walshe [18] stated that the tone in the striated muscle of patients with the parkinsonian syndrome is of unvarying intensity through the fullest possible range of shortening and lengthening. This appears to be true of the bladder, where the pressure is high when the bladder is empty and throughout filling. Walshe also showed that rigidity in the parkinsonian patient was dependent on the reaction to stretch but that the stretch responses were not increased.

Perhaps the best illustration of increased tone in the vesical muscle of patients with Parkinson's disease is shown in figure 5. The bladder made no effort to accommodate in order to hold increased quantities of fluid at low pressures. With the addition of increments of fluid the resting intravesical pressure rose by a series of steps. The fall to a resting pressure was slow. The bladder behaved as if the wall was elastic.

Several of the graphic records show that the contractile power of the bladder raised the pressure to abnormally high levels. The external sphincter, a striated muscle, often offered unusual resistance to passage of the catheter. The increased height of the final contraction of the vesical muscle may be related to the hypertonicity of the external sphincter muscle. The waves of contraction were well sustained so that the bladder was emptied completely and no residual urine was collected. As the response to stretch was not overactive, the complaint of urgency occurred seldom. The decrease in vesical capacity leads to frequency of micturition. This frequency may be overlooked by patients who are accustomed to empty the bladder often.

C. Unusually Large Vesical Volume.—Although the capacity of the bladder was decreased in most patients with the parkinsonian syndrome, it was normal in 1 and greater than normal in another. The latter finding requires explanation. We have observed three conditions in which the vesical capacity is increased: injury of the posterior sacral roots, as in tabes dorsalis; injury of the cerebellum, and the early stage of shock associated with damage to the spinal cord. It is probable that enlargement of the bladder will take place also whenever the afferent pathway carrying the sensation of vesical distention is injured on its way to the cerebral cortex without severe, concurrent damage to the motor pathway. Under these conditions, the patient is no longer aware when the bladder is full, and the wall

18. Walshe, F. M. R.: Physiological Analysis of Some Clinically Observed Disorders of Movement, Lancet **1**:1024, 1929.

becomes passively stretched by the accumulation of urine (Dees and Langworthy [18a]).

The pathway carrying vesical sensation travels upward in the lateral columns of the cord (Barrington [18b]). Here, it would be unlikely to be injured bilaterally without damage to the motor pathways. Above this level little is known concerning this sensory pathway. It appears to end with other sensory pathways in the thalamus. Thus, Dejerine and Egger,[19] in the first classic description of the thalamic syndrome, mentioned vesical tenesmus and frequency of micturition as two of the marked early symptoms. The frequency may have been due to the pain. It is easy to believe that this sensory pathway may be injured bilaterally in the forebrain without great damage to the descending motor pathways. I have as yet given no specific examples of this type of lesion.

Watts and Uhle [20] described disturbances of the bladder in cases of tumor of the brain, most of which were gliomas of the forebrain. Some of the patients had a bladder of unusually large, and others of unusually small, volume. These infiltrating, space-occupying tumors do not give symptoms valuable for studies on cerebral localization, and the variations in vesical volume on both sides of the normal mean are hardly significant unless an explanation can be given. Perhaps one type of lesion damages predominantly the motor, and the other the sensory, side of the reflex arc.

Holmes and Sargent [21] described the symptoms of vesical disturbance at the level of the cortex in their account of thrombosis of the superior longitudinal sinus. In 1 case the patient was incontinent because he was unaware when the bladder was full. In another there were extreme urgency and frequency. The first case suggests involvement on the sensory, and the second on the motor, side of the reflex arc.

There are no reliable quantitative methods for measurement of tone in the striated muscles of man. The graphic records of vesical activity give rough quantitative information concerning tone in the smooth muscle of the bladder. It is, however, not enough to speak of a "hypotonic" and a "hypertonic" bladder (Watts and Uhle [20]) on the basis largely of vesical capacity. This is, at best, an inexact

18a. Dees, J. E., and Langworthy, O. R.: An Experimental Study of Bladder Disturbances Analogous to Those of Tabes Dorsalis, J. Urol. **34**:359, 1935.

18b. Barrington, F. J. F.: The Localization of the Paths Subserving Micturition in the Spinal Cord of the Cat, Brain **56**:126, 1933.

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use of the term "tone." From study of the graphic records I have selected certain criteria by means of which information can be gained concerning tone in the detrusor muscle. These are the capacity, the ability to accommodate quickly to increased volumes, the resting pressure in the empty bladder and during filling and the response of the muscle to sudden stretch. The power of contraction of the muscle is measured by the strength, duration and spacing of muscular contractions and by the intravesical pressure which develops before urine escapes from the urethra.

My colleagues and I have discussed in other papers the relative value of mercury and water manometers in the study of vesical activity. Spontaneous waves of vesical contraction are damped by the inertia of the mercury, whereas they are recorded well with a water manometer. I believe that the importance of these waves in forming an opinion concerning the position and extent of the injury in the nervous system has been proved by recent clinical studies (Langworthy, Lewis, Dees and Hesser [11]).

SUMMARY

Certain patients with the parkinsonian syndrome complain of frequency of micturition. Graphic records of vesical activity may reveal two abnormalities. The resting intravesical pressure is abnormally high both in the empty bladder and during filling. The volume of the bladder is often decreased. The stretch reflex in the muscle is not usually hyperactive. The pathologic changes in these patients are not sharply localized or limited to one group of cells or fibers. For this reason, the records of vesical activity are not exactly similar, as they are after injury of the corticospinal tracts. The discussion is concerned with the explanation for these differences in vesical activity.

CEVITAMIC ACID CONTENT OF BLOOD PLASMA IN ALCOHOLIC PSYCHOSES

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The pathologic lesions in the central nervous system associated with chronic alcoholism may be divided into two groups; (*a*) pellagroid and neuritic changes, described by Meyer [1] as central neuritis, and (*b*) the lesions described by Wernicke [2] as polioencephalitis haemorrhagica superior and inferior. Wernicke's disease was further studied by Gamper [3] and Tsiminakis [4] with respect to the predominance of the lesions in the mamillary bodies and their surroundings. The mineral content of these lesions has recently been investigated by Alexander and Myerson,[5] and the vascular pattern, by Campbell, Alexander and Put-

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From the Division of Psychiatric Research, the Boston State Hospital; the Surgical Laboratory, the Peter Bent Brigham Hospital; the Neurological Unit, Boston City Hospital, and the Department of Neurology, the Harvard University Medical School.

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nam,[6] who observed varicose deformities, stasis and perivascular hemorrhages in the affected areas. One of us (L. A.) [7] had the opportunity to observe a patient with Wernicke's disease following chronic alcoholism who had clinical and pathologic evidence of scurvy, characterized by subperiosteal, intramuscular, subcutaneous and perifollicular hemorrhages.

It is generally conceded that patients with chronic alcoholism usually have poor dietary habits, which may lead to a state of panavitaminosis. Since the hemorrhages occurring in Wernicke's disease may conceivably bear some relation to those observed in scorbutic patients, we thought it of interest to study the cevitamic acid content of the plasma in patients suffering from alcoholic psychoses, which constitute the group in which the lesions described by Wernicke may be expected to be seen at necropsy.

Investigations on the cevitamic acid content of the blood and spinal fluid have previously been made by Plaut [8] on a general group of patients suffering from various psychoses. Among these patients was a small group with alcoholic psychoses who showed low values for cevitamic acid in the blood and spinal fluid. Plaut carried out the determinations of vitamin C in the various biologic fluids by a spectrophotometric technic; although his method has proved to be one of the most reliable, he did not take into account the effects of oxidation of cevitamic acid. On the other hand, Pijoan, Townsend and Wilson [9] showed that oxidation of cevitamic acid occurs rapidly in the blood after it has been withdrawn. In order to avoid this loss, which would account for some of the low cevitamic acid levels of the plasma reported in the literature, we used the method devised by Pijoan and Klemperer [10] in our studies on the blood of fasting patients with alcoholic psychoses.

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MATERIAL

Our material consisted of 106 patients with alcoholic psychoses and 58 patients used as controls. The patients with alcoholic psychoses were divided into three groups. Group A, consisting of 65 subjects, included 5 with delirium tremens, 36 with Korsakoff's psychosis, 5 with acute alcoholic hallucinosis, 15 with chronic alcoholic hallucinosis and 4 with alcoholic paranoid psychosis. All these patients presented a typical textbook picture, in which the psychosis was associated with polyneuritis. Group B included 18 patients in whom the psychosis, according to our clinical experience, had a definite etiologic relation to the excessive use of alcohol but in whom the psychiatric picture was not typical and the polyneuritis was either slight or absent. This group included 2 patients with Korsakoff's syndrome, 5 with acute hallucinosis, 5 with chronic hallucinosis and 6 with alcoholic paranoid psychosis. Group C consisted of 23 patients without polyneuritis but with a substantiated history of severe alcoholism of long standing. The psychosis presented by these patients had originally been diagnosed as alcoholic, but when they were reclassified for the purpose of study, we concluded that the type of psychosis present could be considered only as probably precipitated by chronic alcoholism. In short, alcoholism in this group was not the etiologic factor in the psychosis, but was merely contributory. In this group were 4 patients with a Korsakoff-like syndrome, 3 with acute hallucinosis, 10 with chronic hallucinosis, 4 with an alcoholic paranoid psychosis and 1 with chronic alcoholism complicated by cerebral hemorrhage. In addition, Korsakoff's syndrome existed in a patient suffering from severe chronic alcoholism complicated by pernicious anemia, with combined system disease.

The 58 patients used as controls were divided into three groups. The first, group D, consisted of 33 patients with endogenous psychoses, namely, manic-depressive psychosis and schizophrenia. The second, group E, comprised 9 patients in whom the psychoses were associated with organic disease of the brain, such as dementia paralytica, trauma, epilepsy and mental deficiency. The third, group F, consisted of 16 patients with psychoses associated with cerebral arteriosclerosis and senility. The patients serving as controls were selected (1) to control adequately the dietary influence of hospitalization under the same conditions on the two types of patients and (2) to determine the possible effect of (*a*) age and (*b*) arteriosclerosis and undetermined factors, such as stupor and refusal of food, which may exist in similar psychotic states. The essential difference between the subjects used as controls and the group of patients with alcoholic psychoses was that the latter presented a history of severe alcoholism of long standing with, presumably, a poor dietary regimen.

RESULTS

The cevitamic acid contents of the plasma for the aforementioned groups are represented in the accompanying table.

The normal range for the cevitamic acid content of the plasma for 100 normal subjects on generally accepted balanced diets was found by Pijoan and Klemperer to be from 0.76 to 1.3 mg. per hundred cubic centimeters. It was shown further that the cevitamic acid content for patients with subclinical scurvy ranged from 0.26 mg. per hundred cubic centimeters to the levels found for scurvy of 0.02 mg. or less. "Sub-

clinical scurvy" is a broad term, and possibly a misnomer, as in some instances the cevitamic acid value for the plasma may reflect only a dietary deficiency and not an actual tissue deficiency. From the table it

Cevitamic Acid Contents of the Plasma for Six Groups of Psychotic Patients

Group	Classification	No. of Patients	Average Age, Yr.	Average Plasma Cevitamic Acid Value, Mg. per 100 Cc.	Corrected Means for Plasma Cevitamic Acid Value, Mg. per 100 Cc.	Period of Abuse of Alcohol Prior to Admission, Yr.	
						Average	Means
Group A: Alcoholic psychoses with polyneuritis	.....	65	56 (35-75)	0.576 (0.147-1.364)	0.497	21 (5-45)	20
	Delirium tremens.....	5	51	0.38 (0.28-0.52)	0.346	30 (26-34)	31
	Korsakoff's psychosis	36	57	0.657 (0.147-1.364)	0.538	20 (5-45)	20
	Acute alcoholic hallucinosis	5	55	0.677 (0.572-0.924)	0.58	27 (20-30)	30
	Chronic alcoholic hallucinosis	15	57	0.651 (0.22-1.32)	0.538	21 (5-44)	20
	Alcoholic paranoid psychosis	4	62	0.516 (0.44-0.612)	0.497	24 (20-28)	24
	Subgroup A: Patients hospitalized less than three months: delirium tremens (5); Korsakoff's psychosis (4); acute hallucinosis (1)	10	49	0.379 (0.147-0.616)	0.372	20 (6-34)	20
Group B: Alcoholic psychoses with slight or no polyneuritis	Korsakoff's psychosis (2); acute hallucinosis (5); chronic hallucinosis (5); alcoholic paranoid psychosis (6)	18	53	0.559 (0.281-0.77)	0.537	14 (5-33)	15
Group C: Psychoses probably precipitated by chronic alcoholism with no polyneuritis	Korsakoff's syndrome (4); acute hallucinosis (3); chronic hallucinois (10); alcoholism with complications (2); paranoid psychosis (4)	23	53	0.92 (0.396-1.4)	0.828	14 (2-48)	16
Group D: Controls	Manic-depressive psychosis and dementia praecox	33	40 (20-73)	0.851 (0.212-1.936)	0.717	..	..
	Subgroup D: Patients hospitalized less than three months: manic-depressive psychosis and dementia praecox	10	27 (20-40)	0.893 (0.678-1.185)	0.849	..	..
Group E: Controls	Psychoses associated with organic disease of brain (dementia paralytica, trauma, epilepsy, etc.)	9	42 (19-69)	0.702 (0.423-1.413)	0.616	..	..
Group F: Controls	Senile psychoses and psychoses with cerebral arteriosclerosis	16	63 (59-75)	0.511 (0.381-0.846)	0.459	..	..

will be noted that the average cevitamic acid value for the patients in group A was 0.576 mg. per hundred cubic centimeters, with a mean corrected value of 0.497 mg.; in group B the average cevitamic acid

value for the plasma was 0.559 mg. per hundred cubic centimeters, with a mean corrected value of 0.537 mg. On the other hand, in group C, in which the psychoses were only possibly precipitated by alcoholism, with no associated polyneuritis, the average cevitamic acid content of the plasma was 0.92 mg. per hundred cubic centimeters, with a mean corrected value of 0.828 mg. It is of interest to note that for patients studied shortly after admission to the hospital (subgroup A) before any degree of change in diet could have had much influence on the cevitamic acid metabolism, the average value for the cevitamic acid content of the plasma was 0.379 mg. per hundred cubic centimeters, with a corrected mean value of 0.372 mg. The average age of patients in group A was 56. For the group studied shortly after admission (subgroup A) the average age was 49. In these age groups one would ordinarily expect fairly high values for the cevitamic acid of the plasma.

The patients used as controls who were studied shortly after admission (subgroup D) had an average for the cevitamic acid content of the plasma of 0.893 mg. per hundred cubic centimeters, with a corrected mean value of 0.849 mg. These results are in contrast to those for the group of patients with alcoholic psychoses who were studied shortly after admission (subgroup A). Control group E contained patients who by refusing food had decreased their vitamin C intake; the same applied to certain patients in control group D who were studied after the first three months of hospitalization. Control group F was made up of aged persons with psychoses in whom diminution of the cevitamic acid content of the plasma was present; however, none of these patients, nor those in control group E, had cevitamic acid values in the range of those for subclinical scurvy.

The individual values for both the patients with alcoholic psychoses and those used as controls are presented in the accompanying charts.

In the chart showing values for the cevitamic acid of the plasma for patients with alcoholic psychoses, it is of interest to note that for 5 patients the cevitamic acid contents of the plasma were in the range found in subclinical scurvy, whereas of all the patients serving as controls the values for only 1 were in this range. This patient was 73 years of age and had been hospitalized for twenty-one years for a manic-depressive psychosis of depressive type. The chart further illustrates that the cevitamic acid values for the patients with alcoholic psychoses studied early after admission (subgroup A) were all below 0.62 mg. per hundred cubic centimeters and ranged from 0.147 to 0.616 mg., whereas the values for the manic-depressive and schizophrenic patients used as controls studied early after admission (subgroup D) were above 0.67 mg. per hundred cubic centimeters and ranged from 0.678 to 1.185 mg.

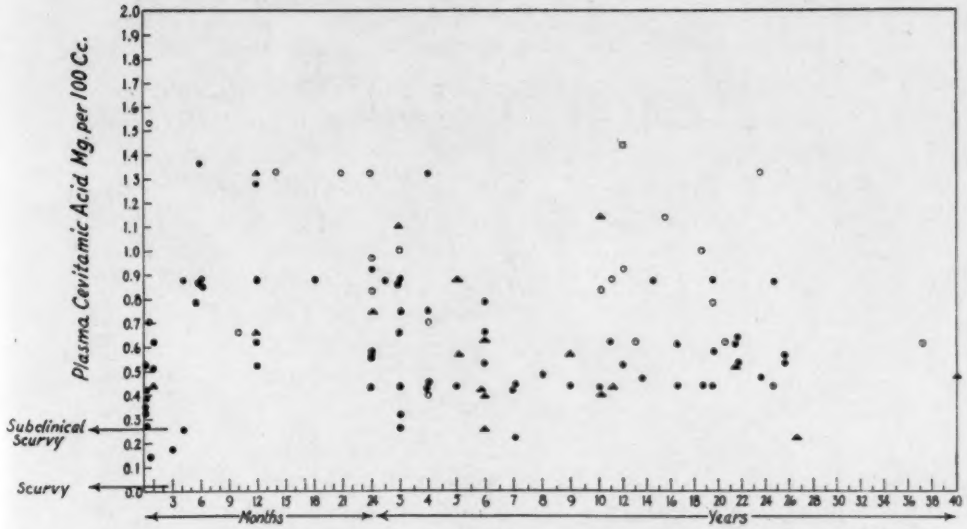

Chart 1.—Data on 106 patients with alcoholic psychoses. In this chart and in the accompanying chart, the time of hospitalization is plotted on the abscissas. Patients in group A, with alcoholic psychoses associated with polyneuritis, are indicated by solid circles; those in group B, with alcoholic psychoses associated with slight or no polyneuritis, by solid triangles, and those in group C, with psychoses possibly precipitated by chronic alcoholism but with no polyneuritis, by hollow circles.

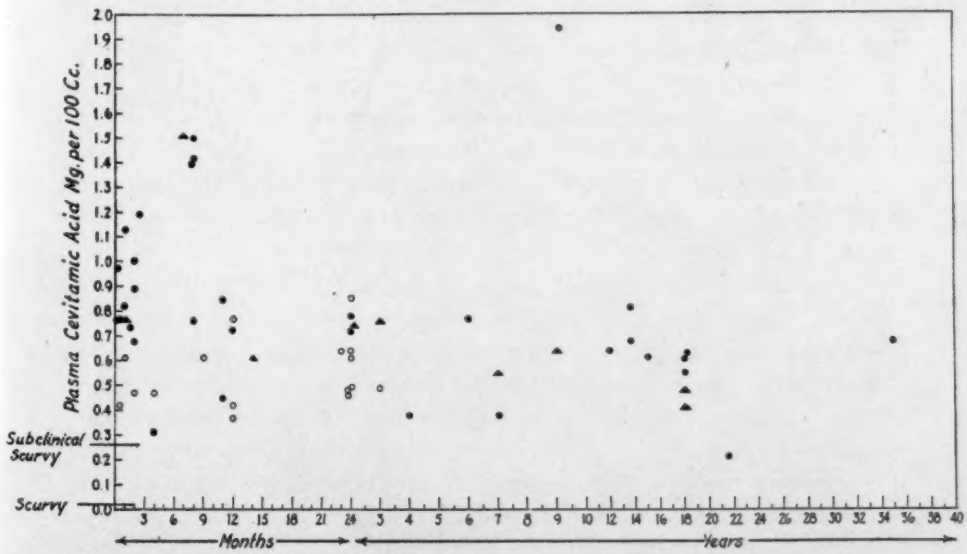

Chart 2.—Data on 58 psychotic patients without alcoholism. In this chart, patients in group D, with manic-depressive psychosis and dementia praecox, are indicated by solid circles; those in group E, with psychoses associated with organic disease of the brain (dementia paralytica, trauma, epilepsy, etc.), by solid triangles, and those in group F, with senile psychoses and psychoses associated with cerebral arteriosclerosis, by hollow circles.

COMMENT

Since cevitamic acid has been identified with vitamin C, the importance of this substance and the methods of its assay have received considerable attention; furthermore, since Wolff [11] has shown that the cevitamic acid content of the plasma has a direct relation to the tissue content of vitamin C, the assay of the vitamin in the blood becomes an important feature not only as an aid in evaluating the cevitamic acid metabolism but as a diagnostic test for scurvy and subclinical scurvy. It must be added, however, that the correlation of cevitamic acid values for the plasma and those for the tissues can no longer be accepted without reservation, for we have found in recent studies that all known methods for the assay of cevitamic acid in tissues are inadequate. Ingalls [12] has demonstrated the significant fact that infection plays an important role in lowering the cevitamic acid content of the plasma and that in scorbutic infants recovering under treatment with cevitamic acid scurvy may again develop in the presence of an infection.

In considering our patients with chronic alcoholism, certain factors must be borne in mind: First, a diet deficient in vitamin C will lower the cevitamic acid content of the blood, as is the case in scurvy. Alcoholism over many years in which the diet is influenced so that insufficient amounts of vitamin C-containing foods are consumed brings about diminution of this vitamin in the body. Second, infection in patients in whom the cevitamic acid content of the tissues is already low will unquestionably diminish the cevitamic acid value to levels found in subclinical scurvy; it is possible to conceive that patients with the cevitamic acid level already on that seen in subclinical scurvy may present scorbutic manifestations. The period of alcoholism in our patients was long; in no case in groups A and B was it less than five years; the mean period for group A was twenty years, and that for group B, fourteen years. Since it is recognized that alcoholism, presumably associated with a diet low in vitamin C, brings about diminution of the cevitamic acid content of the tissues, we feel justified in considering vitamin C deficiency as a predisposing etiologic factor in subdural hematoma in patients with chronic alcoholism. Subdural hematoma is more frequent in this group than can be accounted for by the high incidence of trauma alone. Certain experimental evidence has already been presented to indicate that a relation exists between the formation of

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these lesions and chronic alcoholism. Saltykow,[13] in a review of the literature by numerous investigators who studied experimentally the sequelae of chronic alcoholism, mentioned the occurrence of subdural hematoma in a number of the animals. The incidence of subdural hematoma in hospitalized psychotic patients was studied by Allen, Daly and Moore.[14] Ingalls [15] also noted the occurrence of subdural hematoma in scorbutic patients. The data presented in this communication demonstrate that patients with chronic alcoholism have a diminished cevitamic acid content of the plasma. This may play a role in the diathesis to bleeding which occurs intracranially in association with this condition. However, this study did not include Wernicke's disease, which, though also associated with hemorrhages, has recently been shown experimentally to result from avitaminosis B_1, in the presence of an ample supply of vitamins A, B_2, C and D (Alexander, Myerson and Pijoan [16]).

The values for cevitamic acid in the cerebrospinal fluid were found by us to be similar to those in the plasma (Pijoan, Alexander and Wilson [17]). This finding is in contrast to the observations of Wortis, Wortis and Marsh,[18] who studied this subject by a method different from ours.

CONCLUSION

Patients with chronic alcoholism have a diminished cevitamic acid content of the plasma as compared with persons used as controls. In some instances the cevitamic acid level in the blood is as low as that in subclinical scurvy.

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VARIATIONS IN MAGNESIUM AND POTASSIUM ASSOCIATED WITH ESSENTIAL EPILEPSY

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MINNEAPOLIS

In 1934 we reported [1] a series of clinical cases in which the plasma magnesium was low. Each of the patients had neuromuscular twitchings or convulsions. One was epileptic, and 2 other epileptic patients had values for the plasma magnesium at the lower limit of normal.

Though the chemical aspects of epilepsy have been thoroughly reviewed by Lennox and Cobb [2] and Madsen [3] and the biochemical relations of calcium, magnesium and phosphorus discussed by Schmidt and Greenberg,[4] little is known about the possible variations of magnesium during epileptic convulsions.

Denis and Talbot [5] reported low plasma magnesium in 2 epileptic children, and Blumgarten and Rohdenburg [6] found low serum magnesium in 4 adults with epilepsy.

In view of these observations, particularly the demonstration by Meltzer and Auer,[7] of the anticonvulsant action of magnesium salts,

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This investigation was conducted at the Minnesota Colony for Epileptics, Cambridge, Minn., the clinical material and laboratory facilities of which were placed at our disposal by the Minnesota State Board of Control. The members of this board; Dr. D. E. McBroom, Superintendent of the Minnesota Colony for Epileptics, and Dr. R. W. Brown gave valuable cooperation in this study.

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it seemed possible that lack of magnesium by failure to exert the normal anticonvulsant action, might be an etiologic factor in the convulsive states. This was all the more plausible in light of the results of experiments with lack of magnesium in animals. Hyperirritability and convulsions were produced in white rats and dogs by McCollum and his collaborators [8] and in white rats by Greenberg and Tufts [9] by diets deficient in magnesium, and similar results were obtained in calves by Sjollema and Seekles [10] and by Duncan, Huffman and Robinson.[11] The serum magnesium of these animals was low.

The greater part of the physiologic action of magnesium probably is exerted by the unadsorbed magnesium ions present in the ultrafiltrate, and the variations in the ultrafiltrable magnesium are proportionately greater than those in the total plasma magnesium. We therefore determined both the total and the ultrafiltrable magnesium. Our observations were made on the blood of 79 patients with essential epilepsy, at the Minnesota Colony for Epileptics, 67 of whom were studied during convulsions.

After our present investigation had been completed and the preliminary report [12] published, there appeared an article by Wolf,[13] who found that the magnesium of the whole blood was frequently low in 100 patients with convulsive states, 33 of whom had essential epilepsy. Only 3 of these patients were examined during convulsions; in only 1 was the magnesium below normal. As Wolf determined the magnesium in the whole blood and as Greenberg, Lucia, MacKey and Tufts [14] found that the red corpuscles contain much more magnesium (from 5 to 9 mg. per hundred cubic centimeters) than the plasma, Wolf's figures were higher than those obtained for plasma or serum by other observers.

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The serum calcium remains normal during epileptic seizures, according to Percival and Steward [15] and Griffiths,[16] and our own observations confirm these findings. The sodium also remains normal, according to Lennox and Allen [17] and Madsen,[3] and in a small number of determinations of sodium we obtained the same result.

McQuarrie and his collaborators [18] found that the serum potassium is increased during the convulsions of essential epilepsy. McQuarrie expressed the belief that there is "a leakage of potassium from the cells," that this leakage is accompanied by an increased permeability of the surface of the nerve cells and that this increased permeability is an etiologic factor in the genesis of the convulsions. One of us (A. D. H.[19]) showed that potassium salts antagonize the effects of magnesium salts more potently than do calcium salts, so that an increase in plasma potassium, by antagonizing the anticonvulsant action of the magnesium present, may play a role in the genesis of the convulsions. These effects should depend on the molar ratio of the potassium to the magnesium; since the physiologic actions are probably exerted by the ions, the molar ratio of ultrafiltrable potassium to ultrafiltrable magnesium should be the most significant factor.

ANALYTIC METHODS

We determine potassium and calcium by the methods of Kramer and Tisdall,[20] phosphate by the method of Fiske and Subbarow [21] and dextrose by the method of Gibson.[22] The small number of determinations of sodium were made by the method of Barber and Kolthoff.[23]

In the determination of magnesium we used the colorimetric method which Serles and we described previously,[24] with some modifications. 1. The permanent standard solution of magnesium was prepared by dissolving 10.131 Gm. of magnesium sulfate U. S. P. (analytic grade) in 1,000 cc. of distilled water. 2. Approximately a 1 per cent solution of chemically pure dextrin (from potato starch), freshly prepared by boiling and then cooled, was used as the dispersing colloid. 3. A 4, instead of a 3, per cent solution of ammonium oxalate was used. 4.

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23. Barber, H. H., and Kolthoff, I. M.: J. Am. Chem. Soc. **50**:1625, 1928.

24. Hirschfelder, A. D.; Serles, E. R., and Haury, V. G.: J. Biol. Chem. **104**:635, 1934.

Titan yellow was used exclusively, as we found that Clayton yellow is not as satisfactory.[24a] The 0.1 per cent solution of titan yellow must be kept not longer than two weeks, and the 0.01 per cent solution must be freshly prepared from it on the day of the determination. In order to secure accurate results under the conditions of our determination, the amount of titan yellow used must bear a definite ratio to the amount of magnesium present (0.5 cc. of a 0.01 per cent solution of titan yellow for each 0.01 mg. of magnesium). When less dye is used the result obtained may be too low; when more is used a yellowish tinge may be seen in the colorimeter, the unknown sample does not match with the standard and the result obtained may be too high. The largest amount of dye which gives a pure pink color, without a tinge of yellow, yields accurate results.

In order to obviate this difficulty easily and rapidly, 10 cc. of blood was taken in a centrifuge tube with about 20 mg. of sodium citrate crystals; the tube was stoppered, and the contents were mixed by inversion and centrifuged. To 5 cc. of the supernatant plasma were added 3 cc. of 4 per cent solution of ammonium oxalate and 2 cc. of distilled water; the contents were mixed by inversion, allowed to stand for thirty minutes, centrifuged for ten minutes and decanted from the precipitate.

From this dilute oxalated plasma (2 cc. equals 1 cc. of plasma) 2 cc. aliquot samples were taken. To each of these were added 1 cc. of four-tenths normal sodium hydroxide and 0.01 per cent solution of titan yellow in a series of amounts increasing by 0.01 cc., e. g., 1, 1.1 and 1.2 cc., respectively. To each of these 6, 5.9 and 5.8 cc., respectively of a solution of dextrin was added to bring the total volume up to exactly 10 cc. The contents were mixed thoroughly by inversion and compared with the standard in the colorimeter. The sample which contained 0.1 cc. of solution of titan yellow less than that which just gave a yellowish tinge was used for the determination.

The preliminary determination could be performed also by taking a single 2 cc. sample of oxalated plasma to which 1 cc. of tenth-normal sodium hydroxide, 1 cc. of a 0.01 per cent solution of titan yellow and 6 cc. of the solution of dextrin had been added; to this was added 0.1 cc. of a 0.01 per cent solution of titan yellow, and the contents were again mixed and examined in the colorimeter. The addition of 0.1 cc. portions of a 0.01 per cent solution of titan yellow was repeated until the yellowish tinge appeared; then the determination was carried out with a second 2 cc. sample of oxalated plasma containing 0.1 cc. of titan yellow less than the total amount used in the preliminary procedure.

For ultrafiltrates or plasma the magnesium content of which was low we used a series of aliquot samples to which were added 0.5, 0.6 and 0.7 cc., respectively, of a 0.01 per cent solution of titan yellow, 1 cc. of four-tenths-normal solution of sodium hydroxide and solution of dextrin sufficient to dilute each to exactly 10 cc.

When a low magnesium value was found, the result was always checked by adding a known amount of the mixture of standard solution of magnesium, alkali and dye, redetermining in the colorimeter and subtracting the known added increment of magnesium from the result obtained. Whenever necessary, the standard

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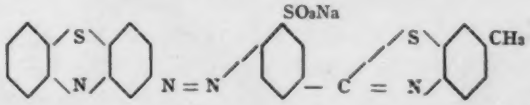
24a. Both titan yellow and Clayton yellow are dyes of the acridine sulfo type (acridine yellow SG). They have approximately the formula,



used for colorimetry was diluted sufficiently to bring the determination within the optimum range of the colorimeter.

When only small samples of blood, ultrafiltrate or cerebrospinal fluid were available, the same procedure could be employed with the microcolorimeter, one-tenth the quantities described being used.

ULTRAFILTRATION

Ultrafiltration of citrated plasma was carried out at a pressure of 60 pounds (27.2 Kg.) per square inch (6.45 cm.) for two hours in a pressure chamber constructed from ordinary plumbing fixtures, at a nominal cost. The membrane used was no. 300 cellophane, the intactness of which was always tested afterward by adding a little solution of congo red or laked blood. The membrane always held back the plasma proteins.

As about 95 per cent of the plasma potassium passes through the no. 300 cellophane membrane and as the error of the method of determination is about 5 per cent, we considered the ultrafiltrable potassium to be practically equivalent to the total plasma potassium.

RESULTS OF DETERMINATIONS

Normal Persons.—For a group of 14 normal subjects we found that the total plasma magnesium varied from 1.8 to 2.4 mg. (average, 2.11 ± 0.11 mg.) per hundred cubic centimeters, the unfiltrable magnesium from 0.9 to 1.3 mg. (average, 1.01 ± 0.12 mg.), the potassium from 17.2 to 24.7 mg. (average, 20.85 mg.), the molar potassium/total magnesium ratio from 5.1 to 7.3 (average, 6.15) and the molar potassium/ultrafiltrable magnesium ratio from 9.9 to 15.4 (average, 12.18). The normal inorganic phosphorus content of the blood was between 3 and 5 mg. per hundred cubic centimeters.

Values for total magnesium of 1.7 mg. and for ultrafiltrable magnesium of 0.8 mg. are, therefore, regarded as low; values for potassium above 25 mg., for the molar potassium/total magnesium ratio above 7.5, for the potassium/ultrafiltrable magnesium ratio above 15 and for inorganic phosphorus of 6 mg. or above are regarded as high.

Epileptic Subjects.—Magnesium and Potassium: During the periods between seizures, when the patient had been free from seizures for several days and would have none for several days, the plasma magnesium was normal in 78 (98.7 per cent) of 79 patients, and the ultrafiltrable magnesium was normal in 77 patients (97.4 per cent). One patient with severe epilepsy had low values for the total and ultrafiltrable magnesium on one occasion two days after a seizure, but normal values at other times; 1 patient with moderately severe epilepsy had low ultrafilterable magnesium on one occasion only, but the total magnesium was always normal and the ultrafiltrable magnesium normal at other times. The potassium was normal in 57 (72.2 per cent) of 79 patients and normal or slightly above normal (under 30 mg.) in 74 patients (93.7) per cent). The molar potassium/total magnesium ratio

was normal for 63 patients (79.7 per cent), and the molar potassium/ultrafiltrable magnesium ratio, for 61 patients (77.2 per cent). The inorganic phosphorus was normal in 68 (97.1 per cent) of 70 patients.

During the convulsions the most characteristic variations from the normal were: low plasma magnesium, especially ultrafiltrable magnesium; high potassium; high potassium/magnesium ratios, and some increase in inorganic phosphates. These abnormalities were most frequent and most intense in the severe forms of epilepsy and less frequent and less intense in the mild forms, though even in the latter there was

TABLE 1.—*Total Magnesium Content of the Plasma of Epileptic Patients*

	No. of Patients*	Mg. of Magnesium per 100 Cc. of Plasma												
		1.2 to 1.3	1.3 to 1.4	1.4 to 1.5	1.5 to 1.6	1.6 to 1.7	1.7 to 1.8	† 1.8 to 1.9	1.9 to 2	2 to 2.2	2.2 to 2.4	2.4 to 2.6	2.6 to 2.8	Above 2.8
Status epilepticus														
Before convulsions	4	..	..	..	..	..	..	..	1	2	..	1	..	..
During convulsions	5	1	1	..	1	..	1	..	..	..	1	..	..	..
After convulsions	5	..	..	1	..	..	2	1	..	1	..	..	..	..
Interim	5	..	..	..	..	..	1	..	1	1	1	..	1	..
Severe epilepsy														
Before convulsions	21	..	..	..	..	1	6	5	..	6	2	1	..	..
During convulsions	27	..	1	3	4	7	6	3	..	1	2	..	..	..
After convulsions	15	..	1	1	..	3	7	3	..	..	..	..	..	..
Interim	26	..	..	..	..	..	1	1	3	10	5	3	3	..
Moderately severe epilepsy														
Before convulsions	15	..	..	..	..	..	1	5	4	5	..	..	..	..
During convulsions	23	..	..	..	..	2	7	4	5	3	1	1	1	1
After convulsions	17	..	..	..	..	..	2	4	6	3	1	1	..	..
Interim	25	..	..	..	..	..	..	1	2	9	6	5	1	1
Mild epilepsy														
Before convulsions	9	..	..	..	..	1	1	3	4	..	..	..	..	..
During convulsions	10	..	..	..	..	..	4	3	3	..	..	..	..	..
After convulsions	8	..	..	..	..	..	1	4	3	..	..	..	..	..
Interim	10	..	..	..	..	..	..	..	..	..	4	5	1	..
Interim (total)	79						2	2	7	32	19	11	3	3

* In this and in the accompanying tables, the numerals represent the number of patients for whom the quantities found lay between the quantities indicated in the column head.
† The heavy vertical line indicates the lower limit of normal.

always some increase in the potassium and in the potassium/magnesium ratios. The same abnormalities were present also, but were less frequent and intense before the convulsions and after the convulsions had subsided. There were no critical levels at which convulsions were certain to occur or to subside. The findings are epitomized in tables 1, 2, 3, 4, 5 and 6.

In 4 (80 per cent) of 5 patients with status epilepticus the plasma magnesium was low during the convulsions, in 2 of whom we encountered the lowest values for magnesium in the entire series (total magnesium, 1.2 and 1.3 mg., respectively, and ultrafiltrable magnesium, 0.5 mg. for both). However, 2 of the patients who had low magnesium during some convulsions also had periods of status epilepticus when the magnesium was normal. The potassium level and the potas-

TABLE 2.—*Ultrafiltrable Magnesium Content of the Plasma of Epileptic Patients*

	No. of Patients	Mg. of Magnesium per 100 Cc. of Plasma										
		Below 0.4	0.4 to 0.6	0.6 to 0.7	0.7 to 0.8	0.8 to 0.9	*	0.9 to 1	1 to 1.2	1.2 to 1.4	1.4 to 1.6	Above 1.6
Status epilepticus												
Before convulsions	4	..	..	..	..	..		..	3	1	..	..
During convulsions	5	2	1	..	..	1		..	1	..	..	..
After convulsions	5	..	..	1	1	1		1	1	..	..	..
Interim	5	..	..	..	..	..		2	2	1	..	..
Severe epilepsy												
Before convulsions	21	..	..	2	6	5		3	3	..	2	..
During convulsions	27	..	4	9	8	3		1	2	..	..	..
After convulsions	15	..	1	4	7	3		..	..	..	..	..
Interim	26	..	..	..	1	..		6	9	7	3	..
Moderately severe epilepsy												
Before convulsions	15	..	..	..	1	7		4	3	..	..	..
During convulsions	25	..	..	1	5	9		5	3	1	..	1
After convulsions	17	..	..	..	..	6		8	2	1	..	..
Interim	25	..	..	..	..	1		3	11	8	2	..
Mild epilepsy												
Before convulsions	9	..	..	..	..	2		6	1	..	..	..
During convulsions	10	..	..	..	..	9		1	..	..	..	..
After convulsions	8	..	..	..	..	6		2	..	..	..	..
Interim	10	..	..	..	..	..		..	2	2	6	..
Interim total	79				1	1		14	29	22	12	

* The heavy vertical line represents the lower limit of normal.

TABLE 3.—*Potassium Content of the Plasma of Epileptic Patients*

	No. of Patients	Mg. of Potassium per 100 Cc. of Plasma											
		15 to 20	20 to 25	*	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	Above 65
Status epilepticus													
Before convulsions	4	1	2		1	..	..	..	..	..	..	..	..
During convulsions	5	..	..		..	..	..	..	3	..	..	..	2
After convulsions	5	..	..		..	1	..	2	1	..	..	..	1
Interim	5	..	5		..	..	..	..	..	..	..	..	..
Severe epilepsy													
Before convulsions	21	1	5		5	8	2	..	..	..	..	..	..
During convulsions	27	..	..		1	1	7	6	6	5	..	1	..
After convulsions	15	..	..		2	6	2	4	..	1	..	..	..
Interim	26	..	12		11	2	1	..	..	..	..	..	..
Moderately severe epilepsy													
Before convulsions	15	..	2		11	1	..	..	1	..	..	..	..
During convulsions	25	..	..		..	5	6	9	2	3	..	..	..
After convulsions	17	..	2		5	5	2	2	..	..	1	..	..
Interim	25	3	14		7	1	..	..	..	..	..	..	..
Mild epilepsy													
Before convulsions	9	..	8		1	..	..	..	..	..	..	..	..
During convulsions	10	..	..		6	4	..	..	..	..	..	..	..
After convulsions	8	..	..		8	..	..	..	..	..	..	..	..
Interim	10	..	10		..	..	..	..	..	..	..	..	..
Interim (total)	79	3	54		12	3	1						

* The heavy vertical line represents the upper limit of normal.

TABLE 4.—*Inorganic Phosphorus Content of the Blood of Epileptic Patients*

	No. of Patients	Mg. per 100 Cc. of Blood			*					
		3 to 4	4 to 5	5 to 6		6 to 7	7 to 8	8 to 9	9 to 10	Above 10
Status epilepticus										
Before convulsions	5	..	3	2		..	..	..	..	..
During convulsions	5	..	..	1		1	1	1	..	1
After convulsions	5	..	1	..		3	..	..	1	..
Interim	5	..	3	1		..	..	..	1	..
Severe convulsions										
Before convulsions	17	1	11	4		1	..	..	..	..
During convulsions	25	..	2	3		10	8	1	1	..
After convulsions	15	..	..	7		7	1	..	..	..
Interim	20	3	12	5		..	..	..	..	..
Moderately severe convulsions										
Before convulsions	15	1	5	6		2	1	..	..	..
During convulsions	21	..	1	8		9	3	..	..	..
After convulsions	18	..	4	11		2	..	..	1	..
Interim	22	5	14	2		1	..	..	..	..
Mild convulsions										
Before convulsions	9	1	8	..		..	..	..	..	..
During convulsions	10	..	1	7		2	..	..	..	..
After convulsions	8	..	4	4		..	..	..	..	..
Interim	10	3	7	..		..	..	..	..	..
Interim (total)	70	15	42	11		1			1	

* The heavy vertical line represents the upper limit of normal.

TABLE 5.—*Molar Potassium/Total Magnesium Ratio for Epileptic Patients*

	No. of Patients	5 to 7.5	*	7.5 to 10	10 to 15	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	Above 45
Status epilepticus												
Before convulsions	4	3		1	..	..	..	..	..	..	..	..
During convulsions	5	..		..	1	1	1	1	1	..	..	..
After convulsions	5	..		..	1	3	1	..	..	..	..	..
Interim	5	4		1	..	..	..	..	..	..	..	..
Severe epilepsy												
Before convulsions	21	7		3	11	..	..	..	..	..	..	..
During convulsions	27	..		..	8	17	2	..	..	..	..	..
After convulsions	15	..		..	8	6	1	..	..	..	..	..
Interim	26	14		10	2	..	..	..	..	..	..	..
Moderately severe epilepsy												
Before convulsions	15	2		7	6	..	..	..	..	..	..	..
During convulsions	25	..		1	19	5	..	..	..	..	..	..
After convulsions	17	..		2	15	..	..	..	..	..	..	..
Interim	25	24		1	..	..	..	..	..	..	..	..
Mild epilepsy												
Before convulsions	9	3		6	..	..	..	..	..	..	..	..
During convulsions	10	..		3	7	..	..	..	..	..	..	..
After convulsions	8	..		6	2	..	..	..	..	..	..	..
Interim	10	10		..	..	..	..	..	..	..	..	..
Interim (total)	79	63		13	2	1						

* The heavy vertical line represents the upper limit of normal.

sium/magnesium ratios were always elevated—more than twice the normal in all instances. The inorganic phosphorus was elevated in 4 patients, in 2 of whom it attained high levels (8 and 9 mg.).

Of 27 patients with severe epilepsy, whose seizures were intense and often occurred in groups, the total plasma magnesium was low in 21 (77.7 per cent) and very low in 6 (22.2 per cent). The value was 1.3 mg. for 1 patient, 1.4 mg. for 3 and 1.5 mg. for 2. However, 6 of the patients who had convulsions when the total magnesium was low also had some convulsions when it was normal, so that 15 patients (55.5 per cent) had convulsions only when the total magnesium was low. Ultra-

TABLE 6.—*Molar Potassium/Ultrafiltrable Magnesium Ratio for Epileptic Patients*

	No. of Patients	8 to 10	10 to 12.5	12.5 to 15	*	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	Above 55
Status epilepticus														
Before convulsions	4	..	2	2		..	..	..	..	..	..	..	..	..
During convulsions	5	..	..	..		..	..	..	1	..	1	1	1	..
After convulsions..	5	..	..	..		..	1	..	1	..	3	..	..	..
Interim.....	5	..	4	..		1	..	..	..	..	..	..	..	..
Severe epilepsy														
Before convulsions	21	..	..	5		4	3	4	5	..	..	..	..	..
During convulsions	27	..	..	..		1	1	2	7	5	3	4	1	3
After convulsions..	15	..	..	..		..	2	3	5	1	2	1	1	..
Interim.....	26	..	11	7		5	3	..	..	..	..	..	..	..
Moderately severe epilepsy														
Before convulsions	15	..	..	1		6	6	1	..	1	..	..	..	..
During convulsions	25	..	..	..		1	5	10	3	3	3	..	..	..
After convulsions..	17	..	..	..		1	6	8	2	..	..	..	..	..
Interim.....	25	2	8	8		7	..	..	..	..	..	..	..	..
Mild epilepsy														
Before convulsions	9	..	..	1		8	..	..	..	..	..	..	..	..
During convulsions	10	..	..	..		1	8	1	..	..	..	..	..	..
After convulsions..	8	..	..	..		2	6	..	..	..	..	..	..	..
Interim.....	10	..	9	1		..	..	..	..	..	..	..	..	..
Interim (total)..	79	2	39	20		15	3							

* The heavy vertical line represents the upper limit of normal.

filtrable magnesium was low in 24 patients (88.8 per cent) and very low in 9 patients (33.3 per cent), being 0.4 mg. in 1 patient, 0.5 mg. in 3 patients and 0.6 mg. in 6 patients. Three of these patients also had convulsions when the ultrafiltrable magnesium was high, but 21 (77.7 per cent) had convulsions only when the ultrafiltrable magnesium was low. The plasma potassium content and the potassium/magnesium ratios were above normal for all 27 patients, the potassium value for 18 patients (66.6 per cent), the potassium/total magnesium ratio for 19 patients (70.4 per cent) and the potassium/ultrafiltrable magnesium ratio for 26 patients (96.3 per cent) being more than twice the normal.

The total magnesium was low in 10 patients with mild epilepsy and was only slightly low (1.7 mg.) in 4 (40 per cent); the ultrafiltrable magnesium was low, but only slightly below normal (0.8 mg.), in 9

patients (90 per cent). The potassium was above normal in all these patients, but never reached 35 mg. The potassium/total magnesium and potassium/ultrafiltrable magnesium ratios were also all elevated, but never greatly. The phosphate level reached 6 mg. in only 2 patients, but never higher.

For the patients with moderately severe epilepsy the findings ranged between those for severe and those for mild epilepsy.

The inorganic phosphorus level was elevated in 20 of 25 patients (80 per cent) but attained 8 mg. and over in only 2 (8 per cent).

Calcium: The calcium content of the plasma remained within normal limits during the convulsions in all but 2 of the 67 patients, in whom it was 8 and 8.1 mg., respectively.

Dextrose: The dextrose content of the blood was determined for 27 patients.[25] Hypoglycemia was not encountered before, during or after convulsions. In 5 patients with status epilepticus the blood sugar before the onset of the convulsions was from 95 to 112 mg. per hundred cubic centimeters of blood, and about an hour after the convulsions had begun it rose to from 139 to 190 mg. In 6 patients with severe epilepsy the blood sugar was from 100 to 118 mg. before the convulsions, rose from 115 to 198 mg. during the convulsions and fell gradually to previous levels after the convulsions had subsided. In 13 patients with moderately severe epilepsy the dextrose was from 100 to 110 mg. before the convulsions and rose during the convulsions, but never exceeded 149 mg. In 3 patients with mild epilepsy the sugar was from 96 to 100 mg. before the convulsions and from 115 to 131 mg. during the convulsions.

Our observations, therefore, confirm those of Lennox, O'Connor and Bellinger [26] and many other investigators and indicate that hypoglycemia is not an etiologic factor in essential epilepsy, as was stated by Pigott; [27] they indicate also that any hyperglycemia which may occur is probably the result of the intense muscular exertion and asphyxia.

Cerebrospinal Fluid: In 7 of 8 epileptic patients we found that the total magnesium content of the fluid during convulsions was from 3.1 to 3.7 mg. per hundred cubic centimeters, which is about that found for normal persons by Hamilton,[28] Stary and his associates,[29] Merritt

25. Haury, V. G., and Hirschfelder, A. D.: Proc. Soc. Exper. Biol. & Med. **32**:1658, 1935.

26. Lennox, W. G.; O'Connor, M., and Bellinger, M.: Studies of Metabolism in Epilepsy, Arch. Neurol. & Psychiat. **18**:383 (Sept.) 1927. A considerable literature on the subject is cited also by Lennox and Cobb.[2]

27. Pigott, A. W.: Endocrinology and the Convulsive State, J. M. Soc. New Jersey **33**:86, 1936.

28. Hamilton, B.: J. Biol. Chem. **65**:101, 1925.

29. Stary, Z.; Kral, A., and Winternitz, R.: Ztschr. f. d. ges. exper. Med. **66**:671, 1929.

and Bauer,[30] McCance and Watchorn,[31] Manzani [32] and Schmidt and Greenberg.[4] This value is higher than that for the magnesium of the plasma. The ultrafiltrable magnesium ranged from 1.4 to 2.6 mg. In 1 patient who had been in status epilepticus for one month, during which the plasma magnesium was low, we found that the total magnesium of the cerebrospinal fluid was 2.1 mg. and the ultrafiltrable magnesium 1.1, which were, nevertheless, higher than the values for the plasma magnesium. In this person the potassium of the cerebrospinal fluid reached a high level (25.6 mg. per hundred cubic centimeters), though this is about the normal level of potassium in the plasma. In another patient

TABLE 7.—*Studies on the Cerebrospinal Fluid and Blood Plasma of Epileptic Patients During Convulsions*

Case No.	Type of Epilepsy	Sex		Magnesium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Molar Potassium/Magnesium Ratio	
				Total	Ultrafiltrate			Total	Ultrafiltrate
1*	Status epilepticus....	..	Fluid	3.2	2.6	5.3	18.3	3.6	4.5
			Plasma	2.1	1.0	8.9	41.2	15.1	32.0
2†	Status epilepticus....	M	Fluid	2.1	1.1	4.4	25.6	7.6	14.5
			Plasma	1.2	0.5	9.9	35.8	18.5	44.6
3	Status epilepticus....	F	Fluid	3.4	2.0	4.7	8.7	1.6	2.7
4	Severe.....	F	Fluid	3.7	1.5	...	9.4	1.6	3.9
			Plasma	1.9	0.7	11.6	41.7	13.6	37.0
5	Severe.....	F	Fluid	3.2	1.9	4.0	9.0	1.7	2.9
			Plasma	1.7	0.6	11.3	46.7	16.7	27.1
6	Moderately.....	F	Fluid	3.1	1.4	...	9.4	1.9	4.2
			Plasma	2.1	0.9	12.0	41.1	12.2	26.4
7	Moderately severe...	F	Fluid	3.4	1.8	3.8	9.8	1.8	3.4
			Plasma	1.8	0.9	12.1	41.3	14.3	28.6
8	Moderately severe...	F	Fluid	3.4	1.4	4.7	7.2	1.3	3.2
			Plasma	1.9	0.8	12.0	53.0	17.4	41.2

* Studies were made just at the end of a twenty-four hour period of status epilepticus.
† The patient had been in status epilepticus one month. The specimen was taken during a convulsion.

the potassium content of the cerebrospinal fluid was 18.3 mg., but in the other 7 patients it remained between 7.1 and 9.8 mg. For all 7 patients the potassium/magnesium ratios for the cerebrospinal fluid were much lower than those for the plasma, in 7 instances the molar potassium/total magnesium ratios falling between 1.3 and 1.9 and the potassium/ultrafiltrable magnesium ratios between 2.3 and 4.2. For the 2 patients in whom the potassium content of the fluid was high the potassium/total magnesium ratios were 7.6 and 3.6, respectively, and the potassium/ultrafiltrable magnesium ratios, 14.3 and 4.5, respectively.

30. Merritt, H. M., and Bauer, W.: J. Biol. Chem. **90**:233, 1931.
31. McCance, R. F., and Watchorn, E.: Quart. J. Med. **24**:377, 1931.
32. Manzani, C.: Boll. d. Soc. ital. di biol. sper. **9**:421, 1933; abstracted, Chem. Abstr. **28**:6467, 1934.

The fact that the ratios, even the potassium/ultrafiltrable magnesium ratios, for the cerebrospinal fluid are much lower than those for the plasma, as well as the high values for magnesium and the low values for potassium, militates against the theory that the cerebrospinal fluid is a simple ultrafiltrate from the plasma.

However, it must be admitted that these analyses of the cerebrospinal fluid do not offer evidence that changes in the magnesium and the potassium content are etiologic factors in the genesis of the convulsions.

ADMINISTRATION OF MAGNESIUM CHLORIDE AND POTASSIUM CHLORIDE

In order to determine whether saturation with magnesium would ameliorate the epilepsy, magnesium chloride in doses of 2 Gm. was administered in enteric stearic acid–coated tablets four times daily for three months to 10 patients (5 with severe and 5 with moderately severe epilepsy). This was as much as the patients could tolerate without indigestion or diarrhea.

Examination of the blood as a routine showed a progressive increase of from 0.4 to 0.8 mg. of total plasma magnesium and from 0.2 to 0.7 mg. of ultrafiltrable plasma magnesium during the period of treatment. However, it was not possible to examine the patients at frequent intervals during the day and night. As magnesium is excreted by the kidneys in the course of a few hours, it is probable that these levels were not maintained. Four of the patients, examined during seizures while receiving the treatment, had convulsions when both the total and the ultrafiltrable magnesium were normal, though the potassium level and the potassium/magnesium ratios were elevated.

One patient had seizures with slightly low values for total and ultrafiltrable magnesium (1.7 and 0.8 mg., respectively) and high values for potassium and the potassium/magnesium ratios.

The frequency and severity of the seizures were not appreciably altered by the oral administration of magnesium. In this regard our results differed somewhat from those reported later by Wolf,[13] who claimed to have obtained some benefit from the oral administration of magnesium to patients with essential epilepsy and especially to those with cerebral arteriosclerosis.

On the other hand, we found that a retained rectal enema of 30 Gm. of magnesium sulfate U. S. P.[32a] in 90 cc. of water, a treatment used by Dr. D. E. McBroom,[33] superintendent of the Minnesota Colony for

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32a. All doses for magnesium sulfate are for magnesium sulfate U. S. P. ($MgSO_4 \cdot 7H_2O$).

33. McBroom, D. E.: Unpublished experimental data.

Epileptics, usually aborted a series of convulsions, but the effects were not permanent. Administration of these enemas raised the plasma magnesium to from 3 to 3.5 mg. (highest, 4.3 mg.) within two hours, but within six hours it was no longer elevated.

Magnesium sulfate U. S. P. in doses of 1 Gm. given intramuscularly usually caused an increase in total plasma magnesium to about 4 mg. and almost, but not quite, always caused convulsions to cease.

Although 1 Gm. of magnesium sulfate U. S. P. given intravenously usually stopped the convulsions, a patient who had already shown prodromal symptoms received 2.5 Gm. intravenously; there developed convulsions fifteen and thirty minutes later, in spite of the fact that the plasma magnesium had risen to 7 mg. per hundred cubic centimeters.

To another series of 11 patients potassium chloride in doses of 2 Gm. was administered four times daily in stearic acid–coated tablets for three months. This also did not alter the frequency or severity of the seizures. In this group also the plasma magnesium rose gradually (with an increase of total magnesium of from 0.1 to 0.6 mg. and of ultrafiltrable magnesium of as much as 0.8 mg.). There was no uniform increase in the plasma potassium, and the potassium/magnesium ratios were usually within normal limits. The frequency and severity of the convulsions were not altered.

SUMMARY

1. The plasma magnesium is frequently low during the convulsions of essential epilepsy.

2. The ultrafiltrable magnesium is low more frequently and is proportionately lower than the total plasma magnesium.

3. The plasma potassium increases during epileptic convulsions.

4. The molar potassium/magnesium, especially the ultrafiltrable potassium/ultrafiltrable magnesium, ratio increases during epileptic convulsions.

5. The phosphate and dextrose contents of the blood increase during epileptic convulsions.

6. All these abnormalities are most intense in the severest forms and are less frequent and less intense before and after the convulsions. They tend to return to normal between periods of convulsions.

7. The magnesium and potassium of the cerebrospinal fluid usually remain normal during convulsions.

8. The magnesium content of the cerebrospinal fluid remains higher than that of the plasma; the potassium remains lower.

9. Continuous oral administration of magnesium did not ameliorate, nor did potassium chloride aggravate, the epileptic seizures.

A METHOD OF TESTING CORTICAL FUNCTION AND SENSITIVITY OF THE SKIN

AN AID IN DIFFERENTIATING ORGANOGENIC AND PSYCHOGENIC DISTURBANCES

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Every living organism, by virtue of its biologic structure, reacts to certain stimuli from within and without. In the course of its development as an individual, the organism tends to fit the contours of its environment, i. e., to adapt. One can see this process in the infant as (through the developing nervous system) he meets his environment for the first time and in the adult when he encounters a new situation. This fitting into the milieu, or adaptation, seems to be a property of all living organisms. As one passes from lower to higher forms of life, the adaptation of the organism as a whole is carried out by successively more highly differentiated and specialized tissues, until in the highest vertebrates adaptation is accomplished chiefly by the cerebral cortex.

In the process of adaptation the organism begins to react to substitutes, or signals, for stimuli having congenital connections—to natural or chance fluctuations in the environment concomitant with these congenital stimuli. First, the organism makes an association between the signal and the inborn reaction to the stimulation—synthesis. In further adaptations the organism may be required to differentiate between different, though similar, signals (analysis) or to cease reacting to signals because they have lost their former significance (extinction).

The various tests for intelligence and mental age give a record of the patient's past education and cultural level, as well as an idea of his use of language and his retention of past experiences. By a battery of tests, one can arrive at a satisfactory formulation of the patient's condition. They, however, make no clearcut distinction between retention of past associations and present ability to make new associations. There are, moreover, advantages in a single simple test which is independent of the subjective state of the examiner and which gives quantitative results.

The following method is designed not as a substitute but as a supplement to ordinary neurologic and psychiatric tests. To use it in lieu of a complete examination would defeat the purpose for which it is

From the Phipps Psychiatric Clinic, Johns Hopkins University.
Read at a meeting of the Neuropsychiatric Section of the Baltimore Medical Society, Jan. 14, 1937.

intended. The method of examination to be described is designed to test the present ability of the patient to adapt to a new environment. The adaptive response selected—that of reacting to the signal for a mild electric shock—is one which is present throughout the vertebrates. Although this defense reflex is only one of the many forms of reaction peculiar to the organism, it is of fundamental importance.

METHOD OF CONDITIONED REFLEX TEST

The apparatus is portable and consists of two boards, 14 inches (35.5 cm.) square—the sending, or operator's, board and the receiving, or patient's, board. On the operator's board is an inductorium connected with three dry cells, or a transformer if alternating current is available, and a series of switches (preferably the noiseless knife form). On the patient's board are two brass electrodes, 3 inches (7.6 cm.) square, placed 2 inches (5.08 cm.) apart; a short circuiting switch, and a series of auditory and visual signals, such as a doorbell, a buzzer and 6 volt automobile lights, red, white and green (fig. 1).

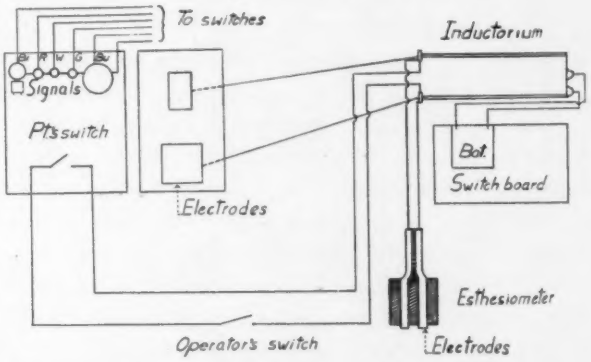

Fig. 1.—Combined ergasiometer and esthesiometer.

The patient is first tested for sensitivity in the two hands. He is asked to place one hand on the electrode and to note the first perception of current in the hand. The coil of the inductorium is moved slowly till the patient reports sensation. Three trials are made with each hand for the purpose of differentiating between the reactivity in (1) successive tests and (2) the sensitivity of the two sides. If there is evidence of difference in sensitivity on the two sides, the whole body may be explored with the esthesiometer, as described later.

Synthesis.—For testing cortical function, the patient is asked to place one hand on the electrodes and to avoid the shock by closing the short circuiting switch before the shock comes as nearly as he can estimate. He is told to watch the board and not to ask questions. A uniform set of brief instructions is given either verbally or in printed form. One of the signals is given for from one to five seconds [1] and is followed by the unconditioned stimulus (shock). Ten trials are given as a routine, more if an exhaustive examination is required. A kymographic record of the latent period may be taken, or it may be recorded

1. The time is varied somewhat with the patient, but in the simplest form of test a uniform duration for the conditioned signal is employed, usually three seconds.

separately with a stop watch. The percentage of the number of correct performances is the patient's score for synthesis. The closeness of the latent period to the time of giving the shock and the quickness of learning must also be considered; more intelligent persons tend to approach the latent period of the signal. A person who learns after two trials, but makes three false closures of the switch, has a score, according to the formula

$$\frac{\text{total number of trials} - (\text{number of trials necessary to learn} + \text{number of false movements})}{\text{total number of trials}} = \frac{5}{10}, \text{ or 50 per cent.}$$

$$\frac{10 - (2 + 3)}{10} = \frac{5}{10}, \text{ or 50 per cent.}$$

Analysis.—A similar signal (for the same receptor organ) is given without following it by the shock. The patient's score for analysis (correct adaptation to the new signal) is computed as before. Ten or more trials are given.

Extinction.—In order to measure the patient's ability to adapt to the changed experimental milieu, the original signal is repeated without the shock till the patient ceases to react.

Retention.—The span of retention may be determined by repeating the test after a given interval, either of minutes or of days. In cases of Korsakoff's syndrome retention may be only for a few minutes; in other cases it may last for days or weeks.

Formulation.—At the end of the test the patient is asked: "How would you explain, in your own words, this examination to a friend; i. e., what happens here?" A correlation is thus made between the verbal learning and learning on the motor level.

PROTOCOLS OF CASES

The following protocols illustrate the results in several cases.

PROTOCOL 1.—Mrs. F. B. B., aged 39, was admitted to the hospital on Nov. 5, 1936, to the service of Dr. Walter Dandy. The diagnosis was hypophysial cyst (confirmed later by operation) with diabetes insipidus and impairment of vision.

Tests with the Esthesiometer (November 5).—The results were as follows:

	Perception			
Sensitivity	First Trial, Cm.	Second Trial, Cm.	Third Trial, Cm.	Pain, Cm.
Right hand	8.75	9.5	9.25	6.25
Left hand	9	9	8.75	6

Tests with the Conditioned Reflex Apparatus.—The results are given in the following tabulation.

Conditioned Stimulus	Duration of Action, Sec.	Conditioned Motor Reflex	Latent Period, Sec.	Intensity of Shock, Cm.
Synthesis				
Red light	5	None	..	6.5
Red light	5	None	..	6.5
Red light	5	+	6	
Red light	5	+	3	
Red light	5	+	6	
Red light	5	+	2	
Red light	5	+	4	
Red light	5	+	4.5	
Red light	5	+	4.5	
Red light	5	+	5	
Analysis				
White light	5	+	5	
Red light	5	+	5	
White light	5	None	..	
Red light	5	−	4	
White light	5	None	..	

Formulation.—The patient stated: "There is a board with two metal plates and some lights and a bell before me. You first test my two hands to see how well I can feel. Then you turn on a light, and after a certain length of time—ten seconds, I think—you turn on the current. I am supposed to avoid the shock when I see the red light. Later you turn on a white light, but I don't get any shock with that, only with the red light."

Comment.—This patient showed no impairment of the cortical function of adaptation within the limits of the test.

Subsequent Course.—The patient was operated on by Dr. Walter Dandy in November 1936 and on Feb. 12, 1937. At the first operation about 5 cc. of mucopurulent fluid was drained from a cyst surrounding the stalk of the hypophysis; at the second operation the right optic nerve was cut, and a tumor weighing 0.02 Gm. was removed from the sella turcica.

On February 21 the patient was given the conditioned reflex test, as on November 5, before the operation. The threshold of sensitivity in the right hand was from 9 to 9.5 cm., and that in the left hand, from 9.2 to 9.5 cm.; the threshold for pain in both hands was 7 cm., which was practically the same as that before operation. There was no impairment of retention in the patient's formulation of the previous test. Conditioned reflexes were formed as readily as in the first test (on the first trial), although auditory, instead of visual, stimuli were used because of impairment of sight. In this patient it is evident that the operation caused no impairment of the functions of synthesis and analysis.

Protocol 2.—J. O. P., aged 23, was admitted on Nov. 17, 1936. The diagnosis was congenital absence of the left frontal lobe.

The results of the tests are given in the accompanying tabulation.

	Perception			
Sensitivity	First Trial, Cm.	Second Trial, Cm.	Third Trial, Cm.	Pain, Cm.
Right hand	11	12	11	8
Left hand	10.25	10.25	10	7.5

There is evident difference in sensitivity on the two sides, corresponding to the cerebral deficiency as determined by roentgenography and operation. The patient was also hypersensitive. The score was only 30 per cent. Although the unconditioned stimulus (shock) was much weaker than that for Mrs. F. B. B. (inductorium at 9 instead of at 6.5 cm.) this patient was hyperreactive.

He performed the "100—7" test in thirty-six seconds, with seven errors.

Formulation.—The patient said: "The test is to see how much you can feel; the lights are to counteract the effect."

Protocol 3.—W. G. B., aged 48, was admitted on Oct. 15, 1936. The diagnosis was postalcoholic (Korsakoff's) psychosis.

The results of the tests were as follows:

Sensitivity	Perception, Cm.	Pain, Cm.
Right hand	5.75	4
Left hand	5.5, 5.5	4

The score was 0.

Formulation.—The patient said: "I put my hand on the plates." "What else?" "I can only make a guess as to what to do." "Why don't you avoid the shock?" "I have no way of telling when the shock is coming."

The last 2 patients showed lack of insight in their formulations. Also, the patient with Korsakoff's [2] psychosis showed diminished sensitivity to both perception and pain with the esthesiometer.

The test as it has been described is the simple form. For a more careful study, details may be added. Thus, for patients with considerable loss of cortical function, one may point out that they are to look on the board for a signal showing when the shock is coming. The complexity of the situation may be increased to any desired extent by using a combination of signals, chain signals and conditioned reactions to time.

ESTHESIOMETRIC TEST

Whenever possible, it is well to replace subjective judgments by an objective test capable of being recorded quantitatively. Thus, instead of estimating the blood pressure by feeling the pulse, one measures the blood pressure in millimeters with a sphygmomanometer, hearing with an audiometer, etc. The ordinary tests for sensitivity of the skin lack precision and require subjective judgments of the examiner. In many cases it is an advantage to have an objective and quantitative record of the patient's cutaneous sensitivity instead of the statement that perception is augmented or diminished. Such a measure can be easily obtained by placing electrodes connected with the inductorium, constructed as shown in the diagram, alternately on corresponding areas of opposite sides of the body. The current is increased until the patient reports the first perception of faradic stimulation. Three tests are made in each spot to obtain the variability of perception. To test the threshold of pain the current is then increased to the limit of tolerance of the patient. Thus one obtains a record of perception, pain and variability.

The accompanying chart (fig. 2) shows the following facts: In the normal subjects there was no difference between the two sides or variability from day to day. In a case of astasia-abasia there were great irregularity in the thresholds and diminution and variability in sensitivity to pain on successive days. In most cases of the Korsakoff psychosis there was regular, but diminished, perception. Both in the cases of the Korsakoff psychosis and in a case of multiple sclerosis in which sensitivity was greatly diminished there was a narrow margin between perception and pain. In a case of congenital absence of the right frontal lobe there was a slight, but constant, difference on three successive days between the thresholds of perception, as well as of pain, on the two sides. In another case of organic disease in which there was a history of a fall on the head five years previously, and weakness on one side

2. In an article by Wendell Muncie, to be published, the cases of Korsakoff's psychosis will be described in detail.

and difficulty in walking until two years before, a slight, though constant, difference in sensitivity to perception and pain was present on the two sides, which was not detected in the usual clinical examination, in spite of the fact that the patient reported that feeling was the same on the two sides. The cases cited are examples of the application of the test.

COMMENT AND SUMMARY

The chief usefulness of such an examination seems to lie in the detection of gross impairment of cortical function, as a quantitative measure of retention, and in the differentiation of organogenic and psychogenic disturbances (found possible with this test in several cases

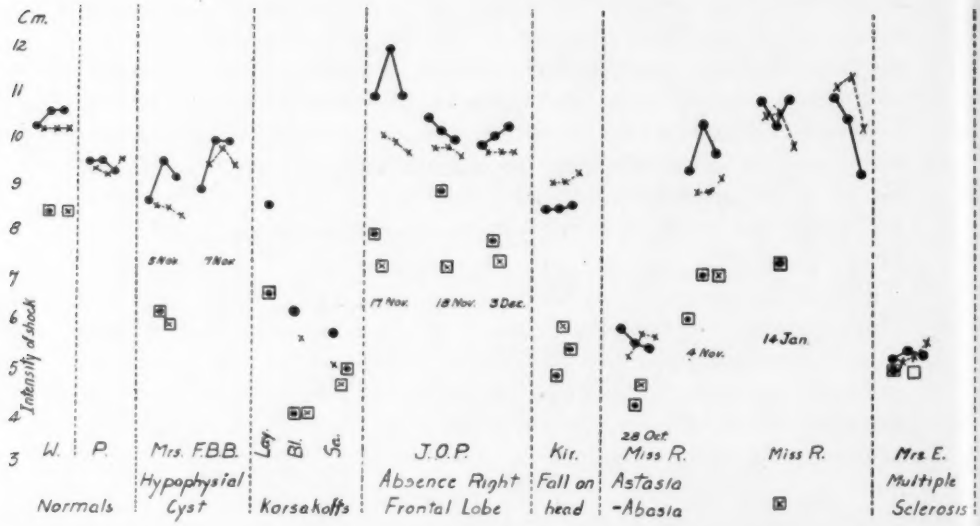

Fig. 2.—Results with the esthesiometric test. In this graph a solid circle indicates sensitivity on the right side; a cross, sensitivity on the left side; a circle in a square, sensitivity to pain on the right side, and a cross within a square, sensitivity to pain on the left side.

in which other means failed). The organogenic forms have also been found to show a greater uniformity of results with both the esthesiometric and the conditioned reflex test. The loss of function is marked in cases of extensive cortical degeneration, such as the Korsakoff and Alzheimer psychoses. Hysterical patients show blocking between verbal and motor learning and lack of uniformity. Frequently, there may be no direct evidence of conditioning, but when there is no overt response the existence of a conditioned connection may be demonstrated by special methods.

Actually, this is a test only of the presence of the defense response of the skeletal muscles to a mild pain stimulus, involving a certain

degree of cooperation of the patient. Although the function tested is a part function, it is also one of adaptation to the environment which is fundamental and generally present throughout the vertebrates, from the fish to man. A fish learns in about one hundred reenforcements of a light by an electric shock that the light means shock, and it moves accordingly. Obviously, the cortex may be damaged without loss of the whole defense mechanism. The test as described is introduced as a standardized empiric method without necessarily involving the underlying theories. It is intended not to grade the intelligence of normal persons but to detect in patients the loss of ability for adaptation to new changes in the environment.

The advantages of the test with such an apparatus as described are that it is standardized and capable of giving quantitative and fairly objective records. What is lost by the limitations is gained in the opportunity to compare results for various patients and for the same patient on successive days, when there is a uniform and controlled set of objective stimuli. Whereas in the intelligence tests no differentiation is made between present ability to adapt and memory, education, retention of past experiences and verbal associations, this method reveals quickly the loss of ability to adapt to the present environment.

Drs. Walter Dandy and Frank Ford permitted use of their clinical material. Dr. Wendell Muncie collaborated with me in the standardization of this test.

DANGEROUS EFFECTS OF THOROTRAST* USED INTRACRANIALLY

WITH SPECIAL REFERENCE TO EXPERIMENTAL PRODUCTION OF HYDROCEPHALUS

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AND
DAVID L. REEVES, M.D.
MONTREAL, CANADA

Thorotrast has recently been advocated[1] as a suitable substance for intracranial injection for diagnostic purposes. Freeman and his associates expressed the belief that the toxic effect is less than that of air and that the substance mixes readily with spinal fluid but is somewhat heavier and therefore visualizes more clearly dependent recesses of the cerebrospinal fluid spaces.

We have been studying its reactions in animals for several months and find it to be a dangerous drug. In moderate doses injected intracranially it produces hydrocephalus, and it concentrates in dependent parts. It is dangerously radioactive, and its elimination from the cerebrospinal fluid spaces is insignificant.

Thorotrast 1073D is a stabilized colloidal suspension of thorium dioxide prepared for intravenous or intracranial use. The original product was modified by Wustmann,[2] with the cooperation of the

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From the Montreal Neurological Institute of the McGill University Faculty of Medicine.

The interest of Dr. W. V. Cone in thorotrast was largely responsible for the present investigation.

* Thorotrast 1073D (Heyden Chemical Corporation) is claimed to be a "stabilized thorium dioxide solution, containing 25 per cent by volume of thorium dioxide, ThO_2 (from 19-20 per cent by weight), and about the same amount of protective colloid (from 16-19 per cent by weight) said to be of a carbohydrate nature and further defined as a dextrin preparation. It contains as a preservative 0.15 per cent of methyl-p-hydroxybenzoate" (Thorotrast: Preliminary Report, report of Council on Pharmacy and Chemistry, *J. A. M. A.* **99**:2183-2185 [Dec. 24] 1932).

1. Freeman, W.; Schoenfeld, H. H., and Moore, C.: Ventriculography with Colloidal Thorium Dioxide, J. A. M. A. **106**:96-101 (Jan. 11) 1936.

2. Wustmann, O.: Experimentelle Untersuchungen über die Reliefdarstellung (Umrisszeichung) des Zentralnervensystems im Röntgenbild durch Thorium-Kontrastmittel, Deutsche Ztschr. f. Chir. **238**:529-567, 1933.

Heyden Chemical Corporation. At first it was not well buffered and produced severe toxic effects when used intracranially. Later a more satisfactory buffer was developed, and by a new technic the particles in the suspension were made smaller.

Thorium is the second heaviest metal and is definitely radioactive. This metal disintegrates in successive stages with the elimination of alpha, beta and gamma rays to form thorium lead.

HISTORICAL REVIEW

The first colloidal preparation of thorium dioxide was used in 1928 by Blühbaum, Frik and Kalkbrenner [3] in bronchoroentgenography. In 1929 Oka,[4] a Japanese physician working in Berlin, first accidentally discovered the outlining of the liver and spleen roentgenographically after intravenous injection of the colloidal thorium dioxide substance called "tordiol." In the same year this work was independently verified by Radt.[5] He improved the preparation, used it clinically and introduced it as "thorotrast."

After a rather wide application of thorotrast in various roentgenologic procedures, it is scarcely surprising that intracranial experiments with this substance were undertaken. Moniz [6] first visualized cerebral structures outlining the cerebral vascular tree by injecting various opaque materials into the carotid arteries. He and others finally adopted thorotrast because of its high radiopacity and the fact that it gives little immediate reaction. Radovici and Meller,[7] of France, in March 1932 and Wustmann,[2] of Germany, were the first to report on the intracranial use of thorotrast.

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3. Blühbaum, T.; Frik, K., and Kalkbrenner, H.: Eine neue Anwendungsart der Kolloide in der Röntgendiagnostik, Fortschr. a. d. Geb. d. Röntgenstrahlen **37**:18-29 (Jan.) 1928.

4. Oka, M.: Eine neue Methode zur röntgenologischen Darstellung der Milz (Lienographie), Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:497-501 (Sept.) 1929.

5. Radt, P.: Eine Methode zur röntgenologischen Kontrastdarstellung von Milz und Leber, Klin. Wchnschr. **8**:2128-2129 (Nov. 12) 1929; Eine neue Methode zur röntgenologischen Sichtbarmachung von Leber und Milz durch Injektion eines Kontrastmittels (Hepato-Lienographie), Med. Klin. **26**:1888-1891 (Dec. 19) 1930.

6. Moniz, E.: Die arterielle Encephalographie als Methode zur Lokalisierung von Hirntumoren, Klin. Wchnschr. **8**:1118-1122 (June 11) 1929; Cerebral Angiography with Thorotrast, Arch. Neurol. & Psychiat. **29**:1318-1323 (June) 1933.

7. Radovici, A., and Meller, O.: Essai de liquidographie céphalo-rachidienne. Encéphalo-myélographie par le thorotrast sous-arachnoïdien, Bull. Acad. de méd., Paris **107**:314-317 (March 1) 1932.

Freeman, Schoenfeld and Moore;[1] Alexander, Jung and Lyman,[8] and Dandy[9] have recently discussed the clinical applicability of colloidal thorium dioxide to ventriculography. The first authors were enthusiastic about their results with the medium. They expressed the belief that the favorable diagnostic results are due to its high specific gravity, its great radiopacity and its miscibility with all body fluids and to the fact that replacement of cerebrospinal fluid with fluid produces fewer untoward symptoms than that with air. Dandy,[9] however, said:

> There is no tumor of the brain causing intracranial pressure, and this includes tumor of the pineal body and tumor of the third ventricle, that cannot be accurately localized by ventriculography. There is never, therefore, in my opinion, justification for the use of opaque material as a means of diagnosis or localization of any tumor of the brain.

INTRACRANIAL USE OF THOROTRAST

When injected into the ventricles, most dyes and suspensions are quickly washed into the subarachnoid space, but not necessarily eliminated. Soluble dyes are quickly absorbed and eliminated, but colloidal suspensions, like thorotrast, are treated as fine foreign bodies, picked up by macrophages and stored in the subarachnoid space. The further excretion of such a material depends on the elimination of the macrophages themselves. This is an extremely slow process.

Quincke[10] in 1872, working with cinnabar (red mercuric sulfide), found that after subarachnoid injection of the material it could be seen to spread through the subarachnoid space of the cranial cavity and the spinal canal. However, it became more concentrated in the dependent portions, particularly in the basal cisterns. It could be followed to the cribriform plate, but no farther. It was seen along the sheaths of the optic nerves and in the episcleral space of Schwalbe. Also, it could be traced to the internal ear, along the cranial nerves and from the spinal nerves to their ganglia. Cinnabar could be seen in all subarachnoid prolongations, but never passed to lymphatics or organs outside the cranial cavity.

Numerous authors have reestablished phases of this work, studying the problem from many angles. Wustmann was one of the first to follow roentgenographic studies of thorotrast with macroscopic and microscopic examinations. In this way, he traced the fine layers of particles in the

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8. Alexander, L. T.; Jung, T. S., and Lyman, R. S.: Colloidal Thorium Dioxide: Its Use in Intracranial Diagnosis and Its Fate on Direct Injection into the Brain and the Ventricles, Arch. Neurol. & Psychiat. **32**:1143-1158 (Dec.) 1934.

9. Dandy, W. E.: Operative Experience in Cases of Pineal Tumor, Arch. Surg. **33**:19-46 (July) 1936.

10. Quincke, H.: Zur Physiologie der Cerebrospinalflüssigkeit, Arch. f. Anat., Physiol. u. wissensch. Med., 1872, pp. 153-177.

sulci of the brain and the sheaths of the nerves and then verified these observations histologically.

Radovici, Bazgan and Meller [11] showed that thorotrast injected into the subarachnoid space is slowly taken up by cells of the meninges (macrophages) and spreads over the subarachnoid space, where some is absorbed and the greater part permanently stored.

CONCENTRATION IN DEPENDENT PARTS

Since thorotrast is a suspension of a salt of one of the heaviest metals, it may be expected to settle in the more dependent portions of the subarachnoid space. Freeman and his associates [1] and others have emphasized this fact, indicating that thorium dioxide when injected in the ventricles is seen to pass quickly into the subarachnoid space and that part of it can be recovered at lumbar puncture. Wustmann [2] said that, in correspondence with its high specific gravity, preparation 1073A [12] collected in the deepest points of the fluid system.

ELIMINATION

The problem of elimination of thorotrast from the cranial cavity is confused because of the various terms and methods used to establish the numerous facts.

After he had eliminated all technical sources of error, Wustmann [2] demonstrated thorium chemically in the blood of the longitudinal sinus within the first three minutes after cisternal injection of the colloidal thorium dioxide. Moreover, on the basis of his chemical and histologic results, he expressed the belief that the pathway of the opaque substance, and with it probably the cerebrospinal fluid, was along the lymphatic channels of the cranial and spinal nerves, the arachnoid coverings and the outlying vessels. That elimination of the substance from the cranial cavity is slight was confirmed by his histologic observation of thorotrast at the base of the brain, in the ventricular recesses and in the subarachnoid spaces of a monkey which one and a half months previously had received a ventricular injection of 3.5 cc. of thorotrast.

In discussing the same subject, Radovici and Meller [13] expressed the belief that the passage of thorium dioxide into the circulation of certain animals had been confirmed by exaggeration of the normal shadows of

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11. Radovici, A.; Bazgan, I., and Meller, O.: Recherches histologiques sur l'encéphalographie liquidienne par le thorotrast, Compt. rend. Soc. de biol. **114**: 207-210, 1933.

12. 1073A was an early preparation of thorotrast.

13. Radovici, A., and Meller, O.: La liquidographie chez l'homme (essai d'encéphalo-myélographie par le thorium colloïdal), Rev. neurol. **1**:541-546 (April) 1933.

the spleen and liver taken from about twenty to thirty days after suboccipital injection. They concluded that the dural sheaths and the arachnoid prolongations which accompany the roots of the cranial and spinal nerves conducted the sleeves of contrasting substance toward the lymphatic channels and into the prevertebral ganglia, as in the classic experiments with injection of dyes into the subarachnoid space (Goldman, Babes and Biva). Because of their histologic observations of large quantities of thorotrast in the subarachnoid spaces as long as nine months after injection, they concluded that any such elimination must be slight.

Jacobi and Löhr [14] observed that after the cisternal injection of thorium dioxide there occurred definite outlining of the lymphatics of the mandible and pharynx and of the lymph nodes, consistent with the classic experiments with dyestuffs of Key, Retzius and others.

Of significance in regard to such injections also is the fact emphasized by Essick [15] and Kubie and Schultz [15a] that it is extremely difficult to perform a lumbar or occipital puncture of the meninges without seepage of the solution or suspension into the tissues surrounding the dural puncture, with subsequent coloration of the regional lymphatics and lymph nodes.

Coe, Otell and Hedley [16] stated: "The medium is eliminated but slowly. A more rapid elimination is believed desirable."

Radovici, Bazgan and Meller [17] showed how the intact pia is a barrier to colloidal particles entering the brain. They emphasized that the soft meninges on the surface of the brain and in the depths of the fissures and convolutions constitute a protective filter against foreign particles. At most, a few particles in the subarachnoid space follow the pial vessels only as far as their entry into the brain. Only when a breakdown of the barrier between the fluid and the brain tissue by meningeal lesion

14. Jacobi, W., and Löhr, W.: Eine neue Methode zur Reliefdarstellung des Zentralnervensystems im Röntgenbild, Deutsche Ztschr. f. Nervenh. **130**:15-22, 1933.

15. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Publication 272, Carnegie Institute of Washington, 1920, pp. 377-388.

15a. Kubie, L. S., and Schultz, G. M.: Vital and Supravital Studies of the Cells of the Cerebrospinal Fluid and of the Meninges in Cats, Bull. Johns Hopkins Hosp. **37**:91-129, 1925.

16. Coe, F. O.; Otell, L. A., and Hedley, O. F.: Thorotrast Encephalography by Cisterna Puncture: Preliminary Report of Experimental Studies, M. Ann. District of Columbia **2**:277-279 (Dec.) 1933.

17. Radovici, A.; Bazgan, I., and Meller, O.: Liquidographie d'un foyer de ramolissement cérébral par le thorotrast sous-arachnoïdien, Encéphale **28**:726-731 (Dec.) 1933.

occurs does thorotrast find conditions favorable for penetration into the depths of the brain.

In a report on experiments with intracerebral injections of colloidal thorium dioxide, Alexander, Jung and Lyman [8] said:

> Free granules of colloidal thorium dioxide are present in the tissue only on the first day and are absent from the second day on. Leukocytes appear on the first day following the injection; they disappear on the second day. The first appearance of the colloidal thorium dioxide in the adventitia and endothelium of the adjacent blood vessels is noted on the second day following the injection; from the third to the fifth day the transport to these blood vessels increases, and after this time it remains stationary . . . Without doubt, the substance is being carried away from the brain by way of the blood vessels.

EXPERIMENTAL INJECTIONS

Mindful of the possible damaging effects of thorotrast when injected intracranially, we carried out experiments on cats, dogs and monkeys demonstrating: first, hydrocephalus; second, precipitation and concentration of the material in the dependent parts; third, radioactivity, and fourth, little if any, elimination. In addition, we were interested in following the distribution of thorotrast in the subarachnoid spaces by means of roentgenographic and histologic methods and studying its excretion from the subarachnoid space.

CATS

Method.—Five cats received injections of 1 cc. of thorotrast, cisternally or ventricularly or by a combination of the two, over a period varying from one to four and one-half months.

1. Cat 1309.—Cisternal injections of 1 cc. of thorotrast were given on January 31, March 27 and April 3—3 cc. in all. The animal died on April 4, approximately twenty-three hours after the last injection. Roentgenograms of the head were taken after the first two injections and of the brain after removal, on April 4.

2. Cat 1310.—Cisternal injections of 1 cc. of thorotrast on February 4, March 27 and April 3 and ventricular injection of 1 cc. on April 7—a total of 4 cc.—were given. The animal was killed on June 16, about four and a half months after the first injection. Roentgenograms were taken after the first two injections and on June 15, prior to the death of the animal. Roentgenograms were also taken of the brain after removal, with the optic nerves and eyes intact. The sectioned brain was likewise studied roentgenographically.

3. Cat 1311.—Cisternal and ventricular injections of 1 cc. of thorotrast were given in the same way and on the same occasions as in the case of cat 1310. The animal died on April 8, the day after the ventricular injection, presumably as a result of increased intracranial pressure associated with the anesthesia. Roentgenograms were taken after the first two injections and after the ventriculographic examination, April 7. Roentgenograms were likewise taken of the brain after removal, with the optic nerves and orbits intact, and of the sectioned brain.

4. CAT 1324.—A ventricular injection of 1 cc. of thorotrast on February 6, cisternal injections of 1 cc. each on March 27 and April 3 and ventricular injections of 1 cc. on April 7 and May 8—5 cc. in all—were given. The cat was killed a few hours after the last injection, on May 8, about three months after the first injection.

Except on April, 3, roentgenograms were taken after each injection. On May 8 roentgenograms were also taken of the entire cat, the brain after removal, with the optic nerves and orbits intact, the sectioned brain and the decalcified nasal bones.

5. CAT 1326.—By means of a burr hole over the parietal area, 1 cc. of thorotrast was introduced into the subarachnoid space on February 6. The animal was killed on March 6. Roentgenograms of the head were taken after the injection and of the brain after removal and section at autopsy.

6-11. CATS 1395 to 1400.—In addition, 6 other cats were given one cisternal injection each of approximately 1 cc. of thorotrast and were killed at varying intervals, up to two and one-half months.

12-13. CATS 1393 and 1394.—For the purpose of control, 2 cats were subjected to ventricular taps without the injection of thorotrast and were killed four weeks and nine weeks later, respectively.

Operation.—Dial was used throughout as an anesthetic. Prior to an injection of thorotrast, an approximately similar amount of cerebrospinal fluid was removed.

Results.—Of the first group of 5 cats, all except cat 1309 showed definite evidence of hydrocephalus. Hydrocephalus, moreover, was fully as pronounced in cat 1326, which received one subarachnoid injection of thorotrast, as it was in those which were given both cisternal and ventricular injections (fig. 1).

Roentgenograms taken two months after the ventricular injection of thorotrast revealed almost complete disappearance of the ventricular shadows. The subarachnoid space, however, was much more distinctly outlined, and the diffuse appearance of the material over the cerebral hemispheres was evident (fig. 2, 6). Roentgenograms of the sectioned brain showed the thorotrast lining the ependymal layers of the ventricles and following the subarachnoid space. Because of its high specific gravity, the material had tended to accumulate in the dependent portions of the brain.

Of the 6 cats which received a cisternal injection of approximately 1 cc. of thorotrast, hydrocephalus of varying degrees occurred in 4. The period of survival of these animals, prior to death or to being killed, was from one week to two and one-half months (fig. 3, 2 and 3). One cat died within a week, as a result of increased intracranial pressure due to the presence of thorotrast or of distemper or of a combination of the two. There was obviously not sufficient time for dilatation of the ventricles in this cat (fig. 3, 1).

In the other animal, cat 1397, which showed no ventricular dilatation two months after injection, incomplete filling of the subarachnoid spaces had occurred. This was evident not only in the roentgenograms taken

after the injection but in those of the brain after removal, in which the thorotrast was almost entirely localized in the left cerebral hemisphere. The optic nerves, moreover, were not outlined. Whether hydrocephalus might have developed in a longer period is, of course, problematic.

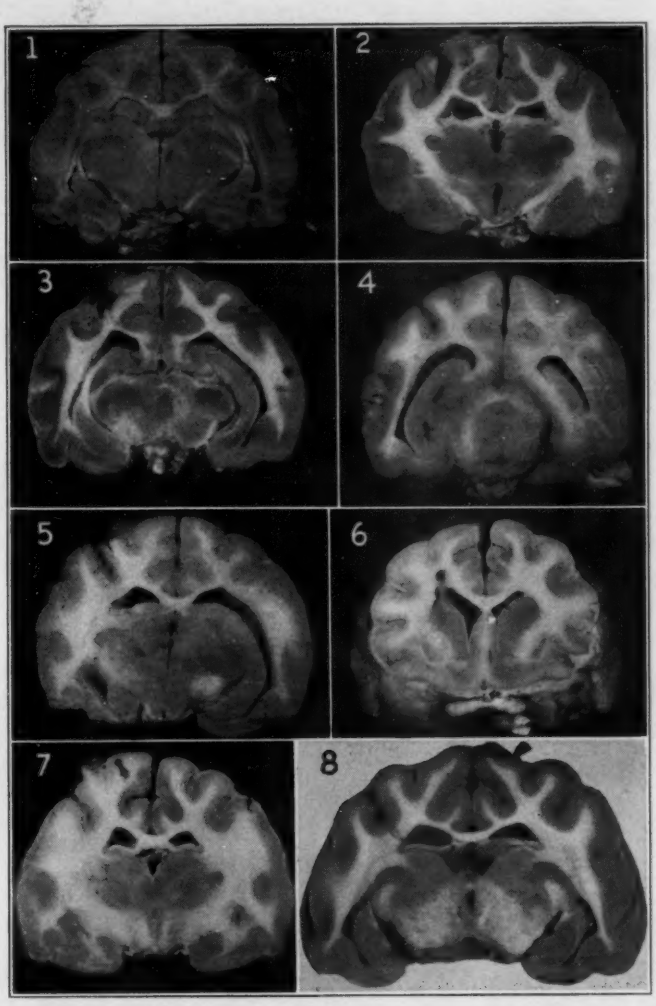

Fig. 1.—Photographs showing development of hydrocephalus in cats following cisternal and ventricular injections of thorotrast. *1* is a section from the brain of cat 1309; *2* and *3* are sections from cat 1310; *4* and *5*, from cat 1311, and *6* and *7*, from cat 1324; *8* is a section from cat 1326. Hydrocephalus is evident in all sections except that for cat 1309.

Moderate hydrocephalus developed in four of the animals during periods of from six weeks to two and one-half months. In all, 1 cc. of thorotrast had more or less definitely outlined the subarachnoid space.

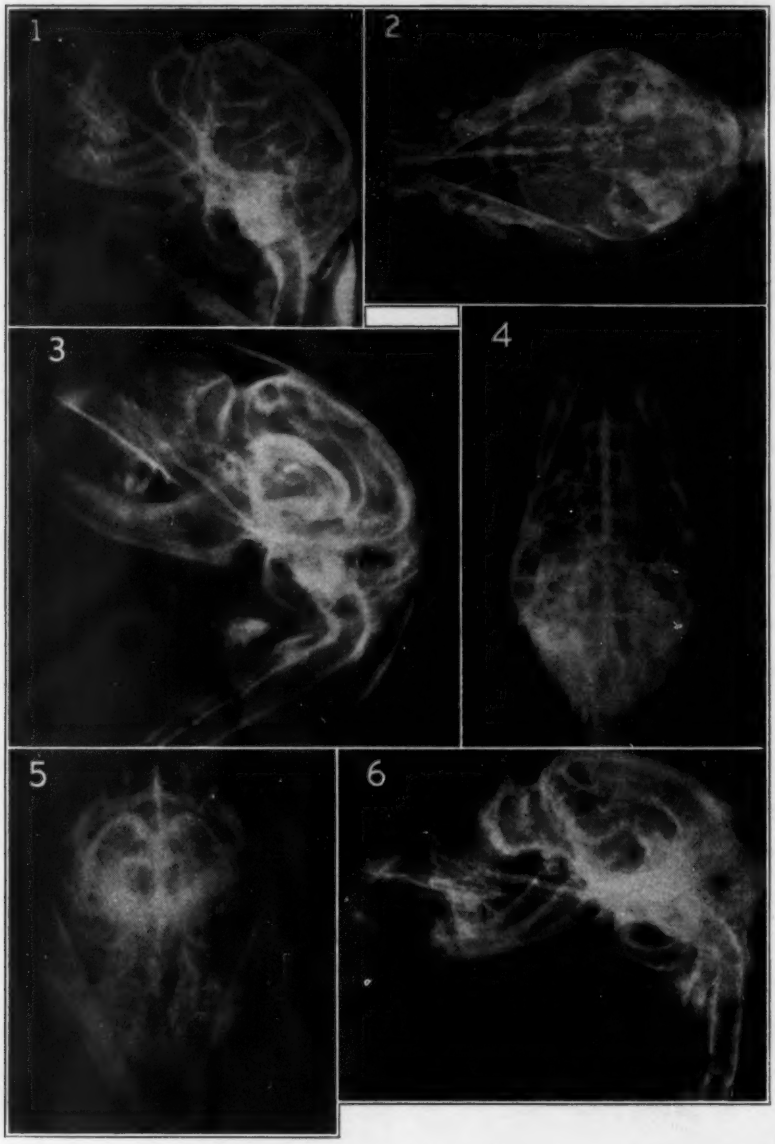

Fig. 2 (cats 1309, 1310 and 1324).—Roentgenograms after intracranial injections of thorotrast. *1* (cat 1309) is a lateral roentgenogram taken after the first cisternal injection of 1 cc. of thorotrast. The convolutions of the cerebral and cerebellar hemispheres are well outlined. *2* (cat 1309) is the basal view taken after the first cisternal injection of 1 cc. of thorotrast, showing the outline of the basilar vessels. *3* (cat 1324) is a lateral roentgenogram taken after the last ventricular injection of 1 cc. of thorotrast, on May 8. Dilatation of the ventricles is shown. Thorotrast is present in the cervical lymphatics and at the muscular and subcutaneous sites of the cisternal injections. The subarachnoid space is also outlined. *4* (cat 1310) is a basal view taken June 15, more than two months after the last ventricular injection of 1 cc. of thorotrast. *5* (cat 1324) is an anteroposterior view taken after the last ventricular injection of 1 cc. of thorotrast, on May 8, showing dilatation of the ventricles. The subarachnoid space over the convolutions of the brain is demonstrated. *6* (cat 1310) is a lateral view taken June 15, more than two months after the last ventricular injection of 1 cc. of thorotrast. The thorotrast has almost completely disappeared from the ventricles. The granular appearance of thorotrast over the cerebral hemispheres is evident.

As a fact, 1 cc. of thorotrast was found to be the smallest amount which could be used satisfactorily to produce hydrocephalus in cats in this short period.

Visualization of the optic nerves invariably occurred. The only exception was cat 1397, in which the subarachnoid space had been faintly and incompletely outlined, owing to an insufficient amount of opaque material injected cisternally.

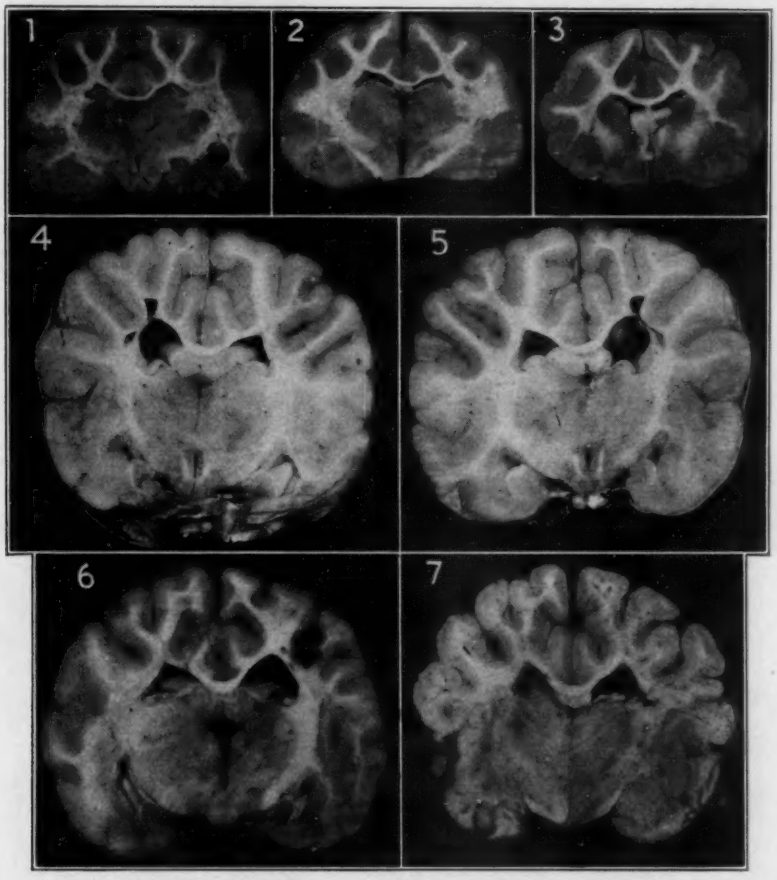

Fig. 3.—Development of hydrocephalus in cats and dogs following cisternal and ventricular injections of thorotrast. *1* shows absence of hydrocephalus in cat 1395, surviving one week; *2*, a slight degree of hydrocephalus in cat 1396, killed two months after injection of thorotrast; *3*, a slight degree of hydrocephalus in cat 1400, killed two and one-half months after an injection; *4* and *5*, apparent hydrocephalus in dog 1258, killed one month after a ventricular injection of 2 cc. of thorotrast; *6*, hydrocephalus in dog 1401, killed two months after a ventricular injection of 1 cc. of thorotrast; *7*, hydrocephalus in dog 1402, killed one and one-half months after a ventricular injection of 1 cc. of thorotrast.

The extension of thorotrast via the fila olfactoria to the nasal cavities was confirmed by the presence of this substance in the roentgenograms taken of the decalcified nasal bones (fig. 4, *2* and *3*).

The ventricles were not demonstrated in the animals given cisternal injections, although in the brains which had been removed and sectioned thorotrast was occasionally seen faintly outlining portions of the ventricular ependyma.

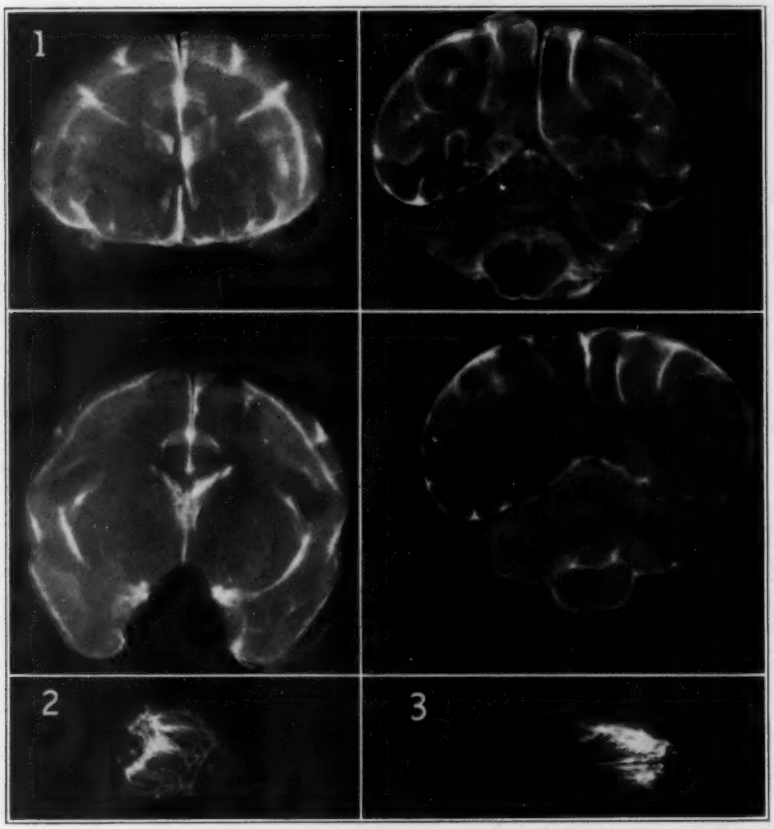

Fig. 4.—Roentgenograms taken post mortem of animals which had previously received injections of thorotrast. *1* (monkey 1342) shows the brain after removal and sectioned thirty-six hours after ventriculographic examination with 6 cc. of thorotrast. The subarachnoid space is seen almost anatomically outlined. *2* and *3* (cat 1324) show the decalcified nasal bone, with deposition of thorotrast.

In most of the animals which received more than one cisternal or ventricular injection of thorotrast, roentgenograms revealed the presence of the substance in the cervical lymph nodes (fig. 2, *3*). The substance was not observed roentgenographically in the cervical lymph nodes of

Fig. 5.—Photomicrograph of a section through the cochlea of a cat given a cisternal injection of 2 cc. of thorotrast and killed five days later. *A* is the ganglion spirale; *B*, the ligamentum spirale; *C*, the ductus cochlearis; *D*, the prominentia spiralis; *E*, the scala vestibuli; *F*, the scala tympani, and *G*, thorotrast within macrophages in both perilymphatic spaces.

the animal (cat 1326) in which thorotrast was introduced into the subarachnoid space through an occipital trephine opening.

Dilatation of the pupils, associated with cachexia, lasting approximately two weeks, occurred in cats 1310 and 1326 and followed the ventricular injection of thorotrast.

The basal and vertebral vessels were outlined in the roentgenograms of cats 1309, 1398, 1399 and 1400 as dark lines contrasting with the white shadow of the opaque medium (fig. 2, *2*).

Roentgenograms taken of the body of cat 1324, on May 8, revealed the external outline of the spinal cord in its entire length. None of the colloidal substance was shown along the spinal nerve roots.

When thorotrast was injected cisternally or ventricularly, there was no significant elimination during the life of the animal. This was evident from the amount of the material remaining in the brains after removal, as seen in the roentgenograms and paraffin sections (fig. 5). There was little difference in the roentgenograms taken immediately after the injections and those taken several months later.

Interestingly, a few adhesions were usually encountered at the site of cisternal injection when the dura was exposed for removal of the brain. Roentgenograms of the dura removed in these cases showed concentration of thorotrast in this region.

Cats 1393 and 1394, used as controls, which had been subjected to ventricular taps without injection of any opaque substance, showed no hydrocephalus when killed.

In order to confirm the assumption that extension of thorotrast along the peripheral nerves is due to an extradural spread of thorotrast after lumbar and cisternal injections, laminectomies were performed on 2 cats under dial anesthesia; the cord was exposed and sectioned, and thorotrast was injected into the subarachnoid space under considerable pressure.

1. Cat 1457.—After transection of the spinal cord, a cannula was inserted into the subarachnoid space of the lower segment and tied securely in place; 5 cc. of thorotrast was injected by syringe under considerable pressure, but a pressure which we thought insufficient to rupture the membranes. Another cannula was similarly inserted into the upper segment, and 6 cc. of thorotrast was injected under considerable pressure by means of a syringe.

2. Cat 1458.—After transection of the spinal cord in the midthoracic region, a cannula was inserted into the subarachnoid space of the lower segment and tied securely in place, and 3 cc. of thorotrast was injected slowly under considerable pressure by means of a syringe. Another cannula was similarly inserted into the upper segment, and 6 cc. of thorotrast was injected under considerable pressure by means of a syringe.

In both animals respirations ceased after injection of about 1 cc. of thorotrast into the upper segment. A few hours later roentgenograms were taken of the entire body and also of the skull. The outline of

the spinal cord was clearly shown; no extension along the peripheral nerves in the region either of the lumbosacral or of the brachial plexus was found. There was likewise no mediastinal opacity, and the cervical lymph nodes were not visualized.

At autopsy the brain, optic nerves, orbits, brachial plexuses and spinal cord were removed intact. Roentgenographic studies of all these were made to determine the presence of the opaque material. The roentgenograms showed that the subarachnoid spaces of the cerebral and cerebellar hemispheres were heavily filled. The ventricles and optic nerves were not visualized clearly until they were sectioned. Previously, they had been obscured by the heavy subarachnoid markings. The opaque material concentrated around the spinal cord and extended

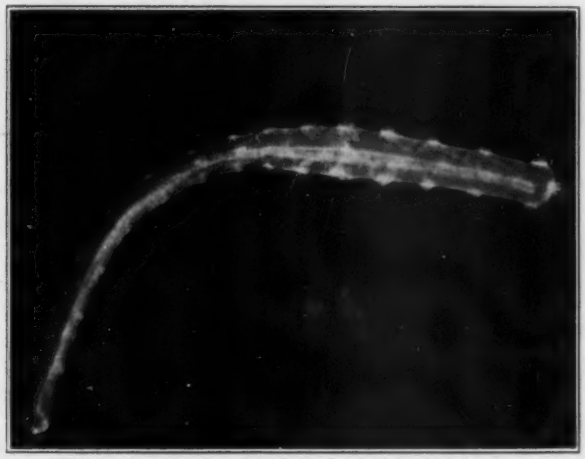

Fig. 6 (cat 1458).—Photograph of a roentgenogram of the spinal cord and brachial plexus after removal, showing absence of extension of thorotrast along the peripheral nerves, in spite of injection into the subarachnoid space under considerable pressure by means of a cannula. The upper cervical portion of the cord was transected after removal of the brain and cord intact.

about 1 mm. toward the nerve roots but not beyond. None could be seen in the brachial plexuses (fig. 6).

Comment.—In view of these findings it is reasonable to conclude that as far as the subarachnoid injection of thorotrast in acute experiments is concerned, the substance does not extend through the closed arachnoid into the perineural spaces of the spinal nerves to any significant degree.

Injection into Peripheral Nerves.—In view of the work of Jacobi and Löhr and others in outlining the peripheral nerves by the injection of thorotrast and of investigations supporting the passage of

injected material and toxins from the spinal and cranial nerves into the subarachnoid spaces, we decided to inject thorotrast into the peripheral nerves of cats.

By means of a small syringe and hypodermic needle, a few cubic millimeters of thorotrast was injected aseptically under considerable pressure into the perineural spaces of the sciatic nerves of cats 1457 and 1458. When the needle was withdrawn, some of the substance extravasated into the tissue spaces. Section and cannulization of the perineural spaces of the nerve would undoubtedly have been a more satisfactory method. The fascia and skin were closed, and roentgenograms of the leg were taken about an hour later.

The roentgenograms revealed the outlines of the sciatic nerve in its entire course along the femur. The opacity did not extend into the region of the lumbosacral plexus. There was no evidence of the

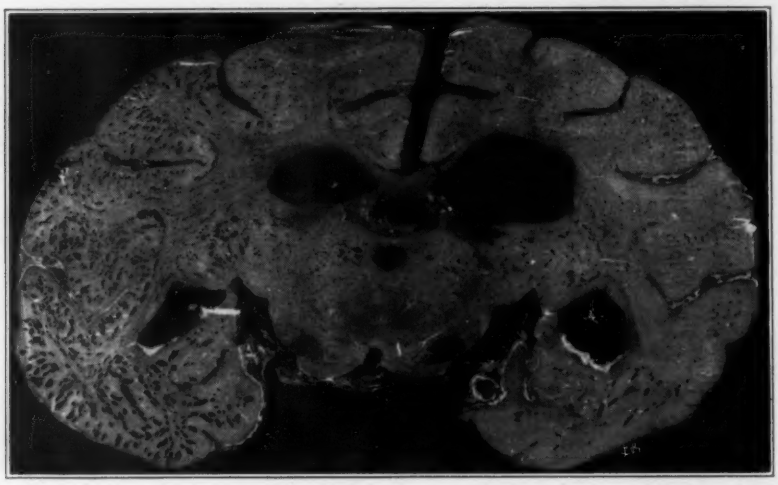

Fig. 7 (monkey 1344).—Photomicrograph of a serial section of the brain. The moth-eaten appearance is due to error in the technic of decalcification. The white material in the subarachnoid space and the dependent portions of the ventricles is thorotrast which has been phagocytosed by macrophages. Hydrocephalus is apparent.

material in the spinal subarachnoid spaces. The extravasations into the tissue spaces at the site of injection were visible in the films. Roentgenograms taken the following day showed no significant alteration from those taken previously.

Subsequent roentgenograms of the spinal cord after removal revealed no absolute evidence of thorotrast in the subarachnoid spaces of the spinal cord.

Suffice it that as far as a substance such as thorotrast is concerned even with high pressures we were not successful in transporting the material either from the subarachnoid space of the spinal cord to the

peripheral nerves or from the peripheral nerves to the subarachnoid space in acute experiments.

DOGS

Three dogs were given ventricular injections of thorotrast. One was killed a month after the injection of 2 cc.; another, six weeks after the injection of 1 cc., and the third, nine weeks after the injection of 1 cc. Prior to these injections

Fig. 8 (monkey 1344).—Autohistioradiograms of paraffin blocks of sections of the brain containing thorotrast, which were developed for one month. Plates used as controls showed no radioactivity and produced no image. Compare with figure 4, *1*.

approximately similar amounts of cerebrospinal fluid were removed. Dial anesthesia was used throughout.

In all 3 animals hydrocephalus developed (fig. 3, *4*, *5*, *6* and *7*). Except for dog 1356, which received 2 cc. of thorotrast, roentgenograms were taken after ventriculography. In each case roentgenograms were taken of the brain after removal and of the sectioned brain.

It is important to take roentgenograms immediately after ventriculography. In dogs 1401 and 1402, of which roentgenograms were taken a few hours after the procedure, the substance had already largely disappeared from the ventricles. The subarachnoid spaces were well visualized and the optic nerves demonstrated. The material had a tendency to accumulate in greater concentration in the dependent areas of the subarachnoid space and ventricular ependyma. In various

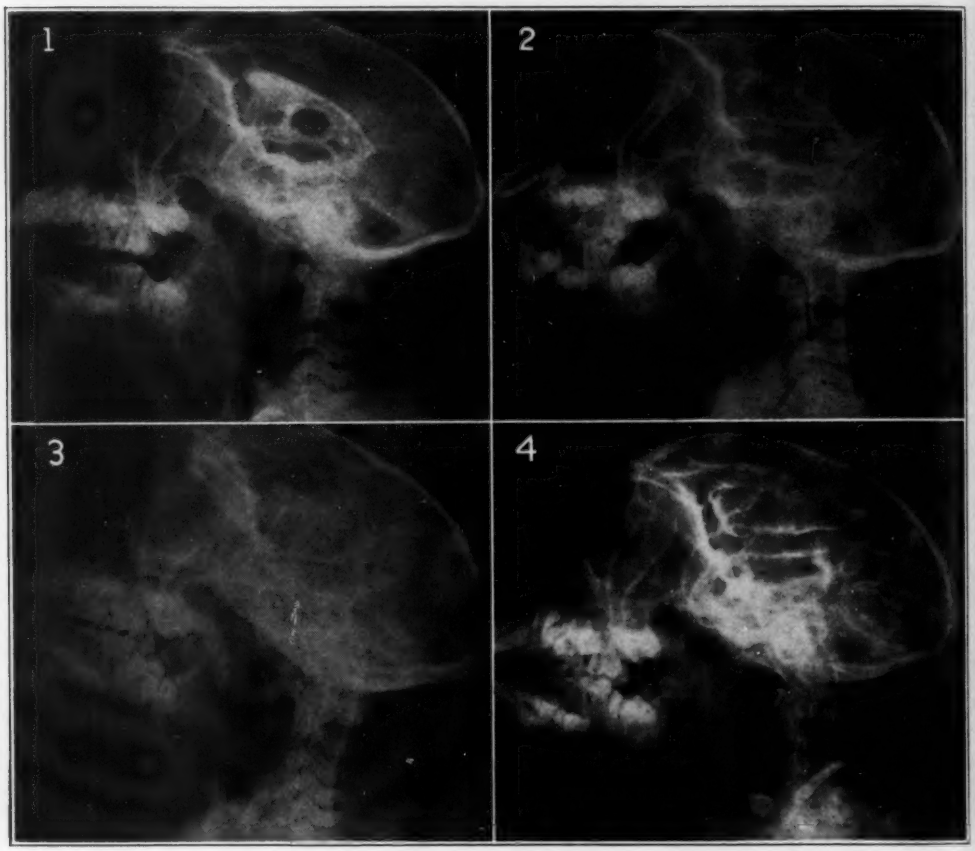

Fig. 9 (monkey 1344).—Roentgenogram showing disappearance of thorotrast from the ventricular system. *1*, is a lateral view taken on April 3, 1936, immediately after ventriculographic examination with 1 cc. of thorotrast; *2*, a lateral view taken one-half hour later than that in *1*; *3*, a lateral view taken one hour later than that in *1*, showing the almost complete disappearance of thorotrast from the ventricular system within one hour, and *4*, a lateral view taken two weeks after the last ventriculogram, on April 16. The presence of thorotrast in the subarachnoid space and the basilar cisterns is evident.

areas over the basilar region of the brain the thorium dioxide had collected in flaky deposits, indicating that it had flocculated to a certain extent.

The cervical lymph nodes of dog 1401 showed little deposition of the thorium dioxide after removal. In none of the 3 animals was there any indication of

significant elimination of thorotrast from the subarachnoid space during the period of survival.

Prior to postmortem examination all the animals had lost weight.

MONKEYS

Six monkeys (Macacus rhesus) received ventricular or spinal injections of thorotrast or both, while under ether anesthesia. Previous to these procedures roentgenograms to serve as controls and encephalograms were taken. Prior to the injection of thorotrast an approximately similar amount of cerebrospinal fluid was removed; the injections were all made under pressure of gravity.

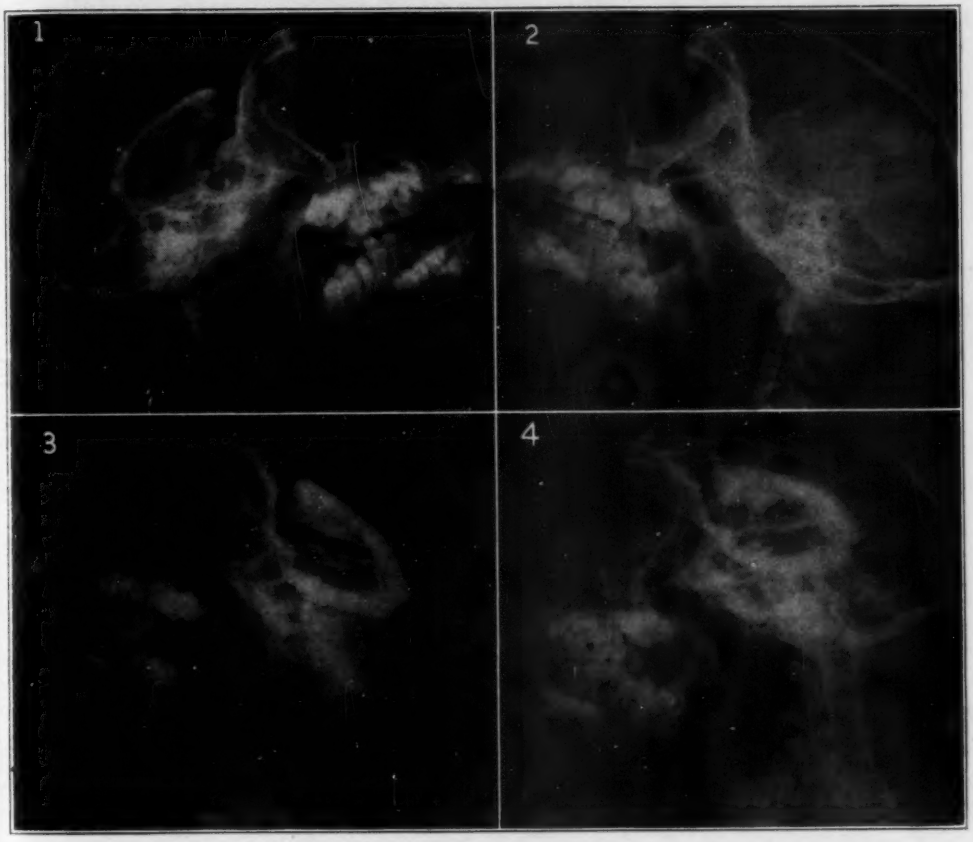

Fig. 10 (monkey 1344).—Roentgenograms showing disappearance of thorotrast from the ventricular system and development of hydrocephalus. *1*, is a lateral view taken after the first ventricular injection of 1 cc. of thorotrast, on March 20, 1936; *2*, a lateral view taken three hours later than that seen in *1*, showing disappearance of thorotrast from the ventricular system; *3*, a lateral view taken immediately after a ventricular injection of 2 cc. of thorotrast, on April 16, showing enlargement of the ventricles as compared with those seen in *1*, and *4*, a lateral view taken one-half hour later than that shown in *3*. The substance has already spread to the subarachnoid spaces. The cervical portion of the spinal cord is more prominently outlined.

1. Monkey 1332.—On Feb. 18, 1936, control roentgenograms and encephalograms were taken. On February 20 a spinal injection of 4.5 cc. of thorotrast was made under pressure of gravity, with the head dependent. When this amount

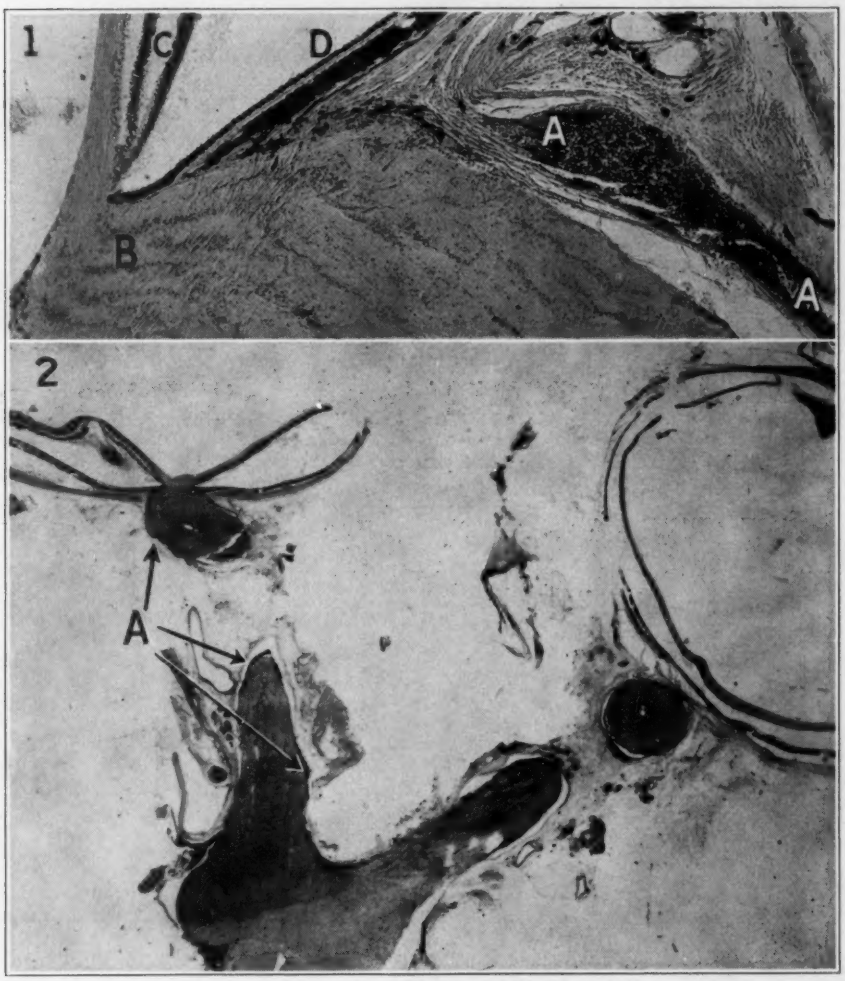

Fig. 11 (monkey 1344).—Photomicrographs of pyroxylin sections showing thorotrast in the region of the optic nerve. In *1*, macrophages (*A*) are loaded with thorotrast; *B* indicates the optic nerve head; *C*, the retina, and *D*, the choroid. In *2*, a horizontal section of the optic chiasm, optic nerves and both eyes, thorotrast, which is shown by the black lines *A*, is contained within macrophages in the perineural spaces.

of thorotrast had been injected, the respirations suddenly became stertorous and then intermittent for about twenty minutes. By means of artificial respiration, the monkey was kept alive until respirations again became normal. Roentgenograms taken immediately showed concentration of the opaque material around the medulla.

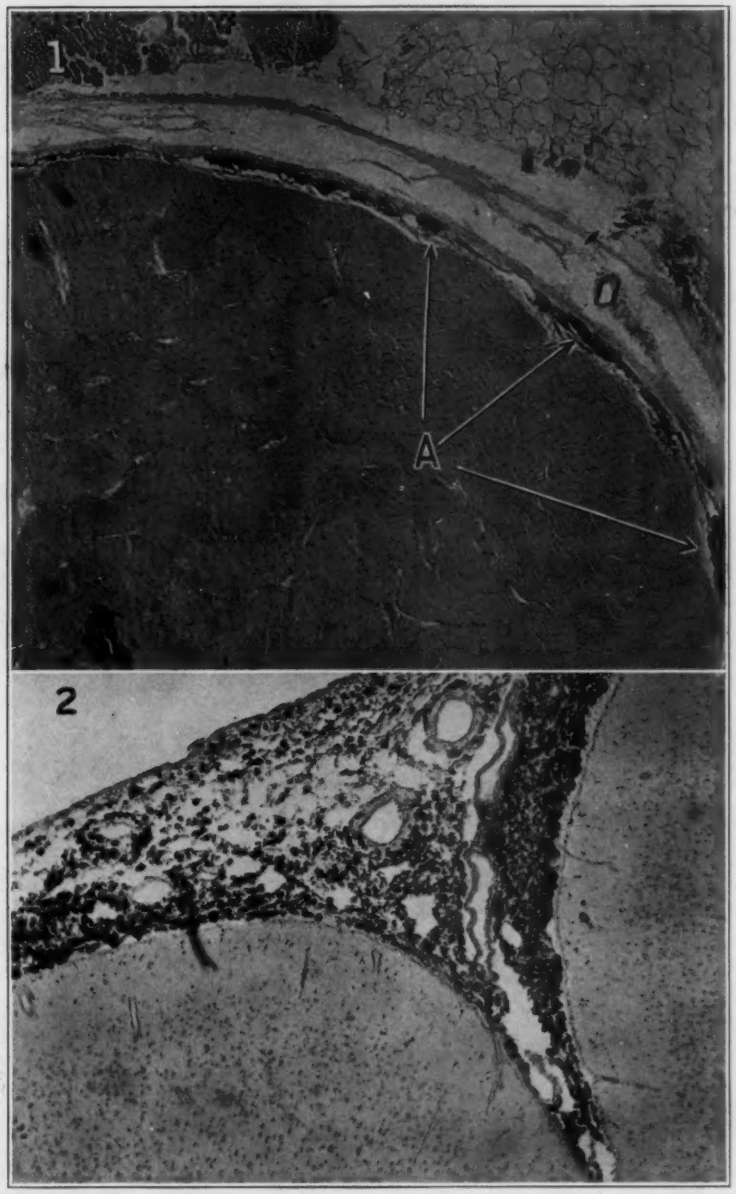

Fig. 12 (monkey 1344).—Photomicrographs. *1* is a cross section of the optic nerve, with thorotrast (*A*) contained within macrophages in the perineural spaces. *2* shows the meninges filled with macrophages which are loaded with thorotrast. Penetration of the substance into the depths of the brain is prevented by the protective barrier formed by the pia mater.

Numerous roentgenograms were taken for several days after this injection. The monkey was accidentally killed on April 4, and careful microscopic studies were made of the nervous system.

2. Monkey 1336.—Control roentgenograms and encephalograms were taken on Feb. 25, 1936. On February 27 a spinal injection of 4 cc. of thorotrast was made, a large portion of the material entering the subdural and extradural spaces.

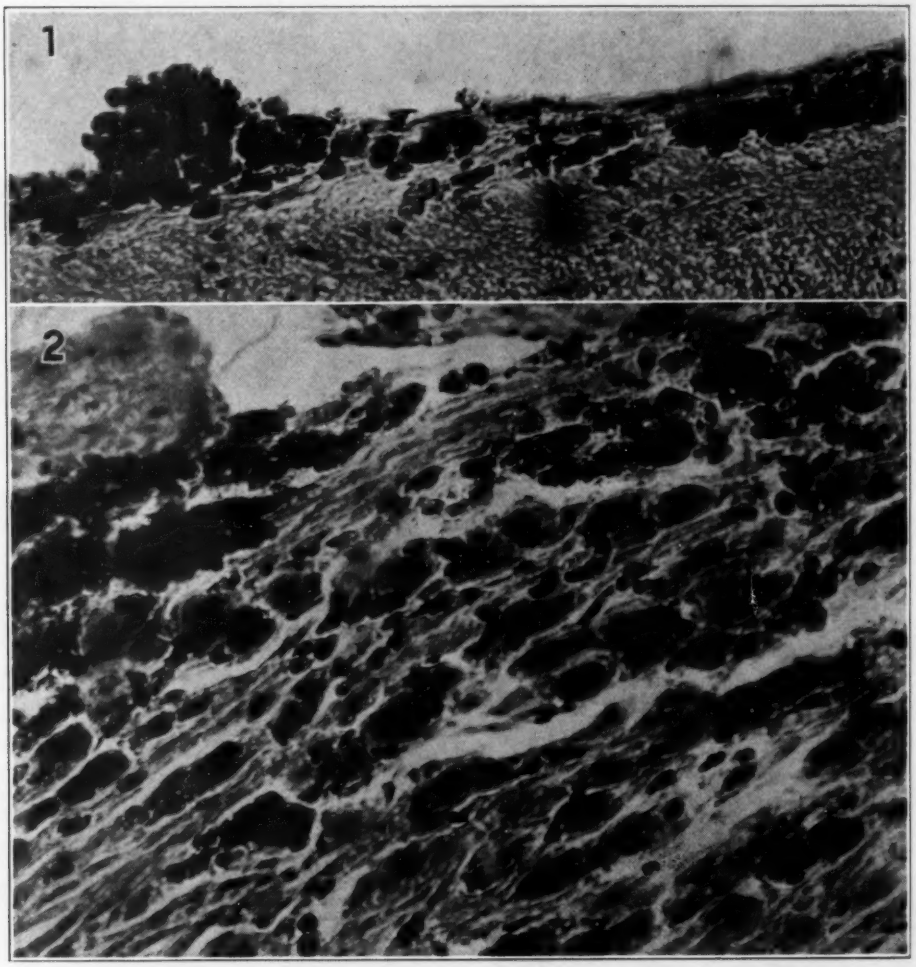

Fig. 13 (monkey 1344).—Photomicrographs. *1* shows the ependymal wall of the lateral ventricle. The macrophages, loaded with thorotrast, are seen organized on the surface as well as forming a conglomerate mass at another site. *2* shows the ganglion of the eighth nerve (large cells), which is infiltrated with macrophages (small cells containing thorotrast).

On March 10 ventricular burr holes were drilled, and on March 16 1 cc. of thorotrast was injected into the ventricles. Again, ventricular injections of thorotrast were made, 2 cc. on May 7 and 1.5 cc. on May 19. Roentgenograms were

taken at various intervals. The monkey was found dead on May 20. Serial frontal sections of the entire head showed moderate hydrocephalus (fig. 7).

3. Monkey 1342.—By mistake no control roentgenograms were taken. On March 3, 1936, bilateral ventricular burr holes were made, and a ventricular puncture was performed. Slowly, by gravity, 6 cc. of thorotrast was allowed to flow into the ventricles. Roentgenograms were taken immediately afterward and at frequent intervals thereafter. The animal survived thirty-six hours.

Roentgenograms taken of the brain, cord, optic nerves and eyes after removal showed that the entire subarachnoid space was well filled (fig. 4). Paraffin sections of serial frontal sections and pyroxylin sections of the optic tract, nerves and eyeballs were made (fig. 8).

4. Monkey 1344.—On March 5, 1936, ventricular burr holes were made bilaterally, and control roentgenograms were taken. On March 20 and April 3 injections of 1 cc. and on April 16 a ventricular injection of 2 cc. of thorotrast were made. In roentgenograms taken of the head and the entire body at frequent intervals after the injection, the ventricular opacity could be seen to fade in about one hour after each ventricular injection (figs. 9, *1, 2* and *3,* and 10).

On April 25 it was noted that the monkey was blind and that the right pupil was larger than the left. This condition remained unchanged until the monkey was accidentally killed in another experiment three weeks later.

The animal was fixed in formaldehyde and the head removed at the cervical region. The head was then frozen, and frontal sections, about 0.5 cm. in thickness, were made with a fine saw. These sections were roentgenographed, photographed, decalcified and roentgenographed again; paraffin and pyroxylin sections were made, and the paraffin blocks were placed on photographic plates and the images developed (figs. 4, *1*; 11; 12; 13, *2,* and 8).

The rest of the monkey's body, from the neck to the pelvis, was sectioned transversely in slabs about 1 cm. in thickness, and these were roentgenographed with a very light exposure for evidence of thorotrast in any of the visceral organs. Thorotrast could be seen in the subarachnoid space of the brain and spinal cord, extending about 1 mm. toward the spinal ganglia, but not in the lymph nodes or other organs.

The liver, spleen, kidneys, bones and lungs of the monkey were then removed. Paraffin sections were made, and the remaining portions of all these organs were ashed. Electroscopic determinations of the ash revealed no detectable radioactivity in any of the organs.

5-6. Monkeys 1414 and 1415.—Ventricular burr holes were made on Sept. 2, 1936, and control roentgenograms were taken. On September 11 a ventricular injection of 1.5 cc. of thorotrast was made in each monkey.

Before these injections were made, excreta (urine and feces) were collected for one week. After the injection of thorotrast the excreta were collected for three months, ashed in an oven and analyzed for radioactivity by means of the alpha and gamma ray electroscopes. No activity could be measured. Further excretion experiments are in progress.

COMMENT

Radioactive substances are chemical elements which are constantly disintegrating to form new elements. In this process of change alpha, beta and gamma rays are constantly given off. Each of these rays has similar definite physical, chemical and biologic properties. Colwell and

Russ,[18] in a review of these properties, discussed: (*a*) photographic action, (*b*) fluorescence, (*c*) ionizing action and (*d*) penetrating power. Duggar [19] reviewed the biologic action.

In this study use has been made of the various properties of these rays to identify the substance (thorium dioxide) under consideration and to understand its action in the tissues. (*a*) First, a radioactive metal may be identified in the tissues in paraffin blocks by placing the blocks on photographic plates. After removal and development of the plates, there will be no image except that of the radioactive deposits in the tissue. Lacassagne and Lattès [20] were the first to describe this method of examination. They located polonium (radium F) in the tubules and glomeruli of the kidneys, as well as in parts of other organs. They called these photographs "autoroentgenograms."

(*b*) The property of fluorescence was not made use of in this study.

(*c*) The ionizing action of these rays is inversely proportional to their penetrating power, with a ratio of about 10,000:100:1 for the alpha, beta and gamma rays, respectively. This gives the alpha ray, with its short path, an intense ionizing power.

Rutherford, Chadwick and Ellis [21] called attention also to the difference in the production of alpha rays in radium and in thorium in equilibrum. Thorium in equilibrium produces 5 alpha particles, as compared to 4 for radium. From either source alpha rays constitute about 95 per cent of the total rays given off.

(*d*) The penetration of these rays is an extremely important fact. Generally the depth of penetration of each of the three rays is proportional to the density of the material through which the rays pass. The penetration of the individual ray is again dependent on the ray in question. The alpha ray, even though it is the most highly ionized and most potent, is the least penetrating. The order of magnitude of the penetrating power of the alpha, beta and gamma rays is about 1:100:10,000, respectively.

The alpha ray, it will be seen, is the least penetrating. It has been estimated [18] that, at the most, it will traverse 8.6 cm. of air and about 32 microns of living matter.[19] In other words, everything being taken

18. Colwell, H. A., and Russ, S.: Radium, X-Ray, and the Living Cell, London, G. Bell & Sons, Ltd., 1924.

19. Duggar, B. M.: Biological Effects of Radiation, New York, McGraw-Hill Book Company, 1936, vol. 1.

20. Lacassagne, A., and Lattès, J.: Localisation histologique du polonium à l'intérieur des organes hémopoïétiques, Compt. rend. Soc. de biol. **90**:485-489 (Feb. 29) 1924.

21. Rutherford, E. R.; Chadwick, J., and Ellis, C. D.: Radiations from Radioactive Substances, New York, The Macmillan Company, 1930.

into consideration, an alpha particle cannot penetrate as much as 1 mm. of living tissue.[22]

(*e*) The biologic properties of these rays were defined most clearly by Duggar,[19] as follows:

> The biological action of radiation may be accounted for by the chemical effects which radiation produces. The sequence of events may be assumed to be (*a*) ionization, (*b*) chemical changes, and (*c*) biological changes. There may then be further chemical changes as a consequence of the first biological changes, and so forth. This view of the process accounts, at least to some extent, for the delay (latent period) in the appearance of the effects of radiation on living organisms. Whatever the mechanism of the biological action of radiation may be, we know definitely that ions are produced in the material, and that the presence of these ions is apt to produce chemical changes or electrical disturbances, which must affect biological processes.

When cells are exposed to the various ionizing rays (roentgen, alpha, beta and gamma), alteration in the cells is almost a constant observation. Duggar [23] summarized these effects as follows:

> The extent to which damage may occur is dependent upon the penetrating and destructive power of the given band of radiation. Any given effect is primarily due to direct damage to cells, and is relative to dosage, and extends over the entire range from minimal damage to immediate or ultimate death of the cell. In producing a specified damage to a given cell type, the total quantity of the dosage, the duration of the exposure and its intensity, and the interval between partitions of dosage, if any, the rate of growth and variations in sensitivity of the cell, as well as its specific sensitivity, are all interrelated. Indirect or secondary damage, through injury to blood vessels or circulation of cell—disintegrating—products is possible.

On the basis of the preceding remarks, one can understand more clearly the results of experimentation with tissue cultures and animals. Zirkle [24] showed an abnormal cell development in spores under the influence of alpha rays. Anderson and Fischer,[25] in experiments with tissue cells in culture irradiated with thorium X, concluded: "With an increase in the intensity of rays there was a corresponding decrease in growth." Fischer,[26] working with tissue cultures and mesothorium, observed definite inhibition of growth, but after a definite "latent

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22. Lind, S. C.: Chemical Effects of Alpha Particles and Electrons, New York, Chemical Catalogue Company, 1921. Colwell and Russ.[18] Duggar.[19] Lacassagne and Lattès.[20] Rutherford, Chadwick and Ellis.[21]

23. Duggar,[19] p. 250.

24. Zirkle, R. E.: Some Effects of the Alpha Radiation upon Plant Cells, J. Cell. & Comp. Physiol. **2**:251-274 (Dec.) 1932.

25. Anderson, H. C., and Fischer, M.: Die Wirkung von *a*-Strahlen auf Gewebekulturen, Strahlentherapie **48**:500-507, 1933.

26. Fischer, A.: Mesothoriumbestrahlung von Gewebezellen in vitro, Strahlentherapie **40**:54-96, 1931.

period." Lacassagne [27] showed that application for forty-eight hours of 25 mg. of unfiltered radium (alpha, beta and gamma rays) produced necrosis with a punched-out appearance in the ear of a rabbit.

On the contrary if we employ the same radioactive source, but purify the radiation by filtering it through 0.5 mm. of lead,[28] the irradiation may be prolonged for 3 days with impunity, and will provoke only a superficial lesion in the form of temporary loss of epidermis and of hair.

Roussy, Oberling and Guérin [29] observed that injection of thorotrast into white rats produced intense tissue *fibrosis* at the site of the injection. Several months later, in many of these animals sarcomas were developing at the site of the most severe fibrosis.

We can now understand some of the damaging effects of the alpha rays when radioactive substances are stored in the body. Such situations are observed in radium dial workers (radium, mesothorium and radiothorium), in those who have drunk radium waters (radium) and in patients who have received thorium X for various therapeutic measures.

Radium dial workers present a unique example of relatively rapid storage of very active radioactive materials. These girls pointed their paint brushes in their mouths in painting luminous watch dials. In spite of the fact that the material used is extremely insoluble, as much as from 10 to 180 micrograms of radium was found to be stored in the tissues of some of these workers. Changes in the blood, radiation osteitis and focal sclerosis of bones were observed in many. Five of Martland's [30] patients and 2 of Flinn's [31] died of osteogenic sarcoma. The sarcomas appeared to develop at the site of the most severe osteitis. The significant fact in all these pathologic conditions is that *for several years the patients enjoyed perfect health and only after five or ten years did symptoms begin to develop.*

Although the limit of tolerance for the average person was formerly thought to be about 10 micrograms of radium, changes in the bones and teeth have been observed in the bodies of radium workers containing the equivalent of from 2 to 4 micrograms of radium. Leake [32] observed roentgenographic evidence of "focal atrophy and focal

27. Lacassagne, A.: Importance of Filtration and Superiority of Pure Gamma Radiation in Radiotherapy of Malignant Tumors, Radiology **13**:95-102 (Aug.) 1929.

28. Filtration of the rays from radium through 0.5 mm. of lead eliminates all alpha rays and only an insignificant amount of the beta and gamma rays.

29. Roussy, G.; Oberling, C., and Guérin, M.: Ueber Sarkomerzeugung durch kolloidales Thoriumdioxyd bei der weissen Ratte, Strahlentherapie **56**:160-167, 1936.

30. Martland, H. S.: The Occurrence of Malignancy in Radioactive Persons, Am. J. Cancer **15**:2435-2516 (Oct.) 1931.

31. Flinn, F. B.: Stimulating Action of Radioactive Deposits in the Body, Radiology **23**:331-338 (Sept.) 1934.

32. Leake, J. P.: Radium Poisoning, J. A. M. A. **98**:1077-1080 (March 26) 1932.

sclerosis" of the mandible in some radium dial workers whose tissues contained 1 microgram of radium.[33] These changes were the earliest detectable lesions; they show the potenial element of danger in the absorption of long-lived radioactive substances.

Besides the local lesions already described, there are several general pathologic conditions that may develop after the ingestion of radioactive substances; for example, anemias, leukopenias, lowered platelet counts with resulting hemorrhages and temporary loss of resistance to infection. Of chief importance, however, is the fibrosis that is so constantly observed.

It has, of course, been known for years that the major response to high voltage roentgen therapy and implantation of radium is death of cells and *fibrosis*. Only recently, fibrosis as a result of the injection of thorotrast has been emphasized. Boeminghaus [34] described a dense connective tissue response to thorotrast extravasated into the parenchyma of the kidney during pyelographic examination. More recently, Fleming and Chase [35] described intense fibrosis locally and in regional lymph nodes following extravasation of thorotrast in the subcutaneous tissue of the cubital fossa when the substance was injected intravenously.

SUMMARY

Thorotrast, as has previously been described, is a colloidal suspension of thorium dioxide. This colloid is widely dispersed and mixes easily with all body fluids up to a concentration of 1:8. In dilutions higher than 1 part to 8 parts of spinal fluid, flocculation of the salt takes place. The metal (thorium) from which this salt is derived is the second heaviest of all metals, and hence precipitated thorium dioxide settles out rapidly. Furthermore, thorium is one of the two major radioactive metals, and thorotrast has repeatedly been shown to be radioactive.

It is not surprising, therefore, that after cisternal injection hydrocephalus was found in some of Wustmann's [2] experimental animals. With fibrosis as one of the chief tissue reactions to thorotrast, it is fair to assume that even more severe cerebral scarring may take place, with resulting epileptic seizures. Because of its weight, this salt tends to collect in the dependent portions of the ventricles and the subarachnoid space; this fact is of the utmost importance. In the erect position the

33. Twenty-five cubic centimeters of thorotrast possesses radioactivity of the approximate equivalent of 1 microgram of radium (Thorotrast: Preliminary Report, report of Council on Pharmacy and Chemistry, J. A. M. A. **99**:2183-2185 [Dec. 24] 1932).

34. Boeminghaus, H.: Zur Beurteilung des Thorotrast als Kontrastmittel in der Urologie, Ztschr. f. Urol. **28**:10-20, 1934.

35. Fleming, A. J., and Chase, W. H.: Effects of Administration of Thorium Dioxide, Surg., Gynec. & Obst. **63**:145-148 (Aug.) 1936.

substance is found around the basal cisterns or at the conus of the spinal cord. Scarring in either of these locations is dangerous.

Scarring may also be due to the particulate (colloidal) nature of thorotrast. Dixon and Heller [36] produced hydrocephalus by cisternal injection of colloidal kaolin in experimental animals.

Storage.—The properties of thorotrast explain many of our clinical and experimental observations. First, thorotrast when introduced into the body anywhere, is treated as a foreign body, picked up by cells of the reticuloendothelial system and stored. The storage may be in lymph nodes, but if the material reaches the general circulation, it is ultimately stored where reticuloendothelial elements are most numerous, that is, in the liver, spleen and bone marrow. When thorotrast is injected intracranially, the macrophages engulf the foreign material and keep it in the cerebrospinal fluid spaces.

We have shown macroscopically and microscopically that granules of thorium dioxide are stored in the subarachnoid space after spinal, cisternal and ventricular injections. Also, we have demonstrated the spread of the colloidal granules through all the ramifications of the cerebrospinal fluid spaces. Previously, we mentioned the work of Quincke, which showed the spread of particulate matter through the subarachnoid spaces. We can now verify these results and show granules of thorium dioxide in macrophages along the optic nerve sheath, in the perilymphatic spaces in the ear, in the ganglion of the eighth cranial nerve, in the sulci and gyri over the surface of the brain (but never in the depths of normal brain substance) and along the olfactory nerve fibers (but not through the cribriform plate) and the spinal cord, extending only a short distance out toward the spinal ganglia (figs. 11, 12, 13 and 5).

Subarachnoid storage has been further verified by the photographic action of this radioactive substance (thorotrast). Paraffin blocks of the brain were placed on photographic plates, and later these were developed. These plates (fig. 8) showed a detailed picture of the subarachnoid space corresponding to the thorotrast in the paraffin blocks. The greatest photographic effect was noticed in the dependent portions of the subarachnoid spaces; this helps to verify the finding that heavy particulate matter in the cerebrospinal fluid pathways tends to settle out and become concentrated in the basal cisterns and at the conus of the spinal cord.

Effect.—To show that the major portion of the radioactive effect of thorotrast is due to the alpha ray, a thin piece of metal, just sufficiently thick to absorb the alpha ray, was interposed between the

36. Dixon, W. E., and Heller, H.: Experimentelle Hypertonie durch Erhöhung des intrakraniellen Druckes, Arch. f. exper. Path. u. Pharmakol. **166**:265-275, 1932.

paraffin blocks and the photographic plate. A much longer interval was necessary to produce any photographic action.

Since the alpha ray has been reported to be destructive to living cells, one may expect damage to brain tissue adjacent to the particles of thorium dioxide. Previous experimental work has shown that the alpha particle penetrates living tissue about 32 microns, the combined width of about five red blood cells (35 microns). From this, one can surmise that many nerve cells and nuclei lie in the possible path of the alpha ray and are destroyed. Particularly, one may expect severe damage in the perineural spaces along the optic nerves. In figures 11 and 12, *1,* can be seen granules of thorium dioxide along the optic nerve sheath to within a short distance of the retina—only the thickness of two or three cells from the rod and cones, which is well within the range of the alpha particle.

Destruction of cells anywhere in the cerebrospinal fluid spaces from radioactive substances may lead to serious pathologic lesions in the brain: fibrosis, hydrocephalus, cicatrices and possibly sarcoma. Adhesions were seen at autopsy almost invariably in our experimental animals. Hydrocephalus was frequent, and in a few instances granulomatous formations were seen on the ependymal walls of the ventricles (fig. 13, *1*). Freeman [1] described ependymitis and formation of granulomas around granules of thorium dioxide following intraventricular injections of thorotrast.

The meningeal response to this foreign material is often pronounced. Monkey 1342, which had received a single large ventricular injection of thorotrast, died thirty-six hours after the injection. The microscopic sections (fig. 4, *1*) showed macrophages filled with thorium dioxide in large numbers, particularly around the basal cisterns. The other animals showed a less severe immediate reaction, but loss of appetite and weight over a more prolonged period.

Several of the animals, later in the experiments, were seen to hold the head with the forelegs, a posture which we attributed to pain in the head, an evidence of increased intracranial pressure or acute meningeal reaction.

Excretion.—In our experimental work we studied by numerous methods the excretion of thorotrast from the cerebrospinal fluid spaces following ventricular, cisternal and lumbar injections. (Extradural spread of thorotrast after ventricular injection was minimal, and in some cases nonexistent; however, this was not true after cisternal and lumbar injections.)

1. Roentgenographic evidence of excretion of thorotrast from the subarachnoid space has proved to be moderately reliable because of the great radiopacity of the material. For this reason, monkey 1344 was

sectioned in thin slabs, and the sections were roentgenographed with light exposure. Nowhere, except in the cranial and spinal subarachnoid spaces, could any extraordinary opacity be seen.

2. The feces and urine were collected from 2 monkeys which had received (*a*) intracerebral and (*b*) subarachnoid ventricular injections of thorotrast. The excreta were dried and ashed, and the residue was examined for evidence of radioactivity by means of the alpha and the gamma ray electroscope. Examination of the total collection of excreta for three months gave entirely negative results.

3. The liver, spleen, kidneys, lungs and long bones of monkey 1344 were ashed and examined for evidence of radioactivity by the two methods just mentioned. In no tissue could any evidence of radioactivity be found.

4. Last, paraffin sections of the organs mentioned were studied for the brown-staining granules of thorium dioxide so commonly seen in the subarachnoid space of these animals. This examination did not reveal any of the material.

CONCLUSIONS

1. Thorotrast is a colloidal suspension of thorium dioxide, easily miscible with all body fluids and productive of an immediate mild inflammatory reaction. Thorium, from which it is derived, is the second heaviest metal and one of the major radioactive metals.

2. Prolonged storage of thorotrast in body tissues has been shown to lead, first, to mild and, later, to intense fibrosis. In experimental animals (white rats) this has been followed by sarcoma.

3. The pathologic effects of this drug are due to (*a*) its particulate nature, (*b*) its great weight and (*c*) its radioactivity.

(*a*) When injected into an animal, the material is treated as a foreign body, picked up by cells of the reticuloendothelial system and stored.

(*b*) The great specific gravity of this substance is important when it is injected in the subarachnoid space, where it tends to become concentrated in the dependent portions.

(*c*) The well known effects of intense ionization on tissues and tissue culture have been reviewed. Of the three ionizing rays emitted by thorium, the alpha ray (or particle) is by far the most destructive.

4. A review of the effects of the alpha particle shows that its destructive action appears to be due to its intense ionization. Since the effect of the alpha ray is blotted out by less than 1 mm. of tissue, it is only by injection or ingestion of radioactive substances that this ray becomes important.

5. Experimentally, we have demonstrated hydrocephalus in cats, dogs and monkeys after spinal, cisternal and ventricular injections of thorotrast.

6. After ventricular injections of thorotrast we have been unable to demonstrate by means of roentgenography, electroscopic examination of excreta and various organs of the body and microscopic studies of tissues any excretions of this material from the cranial cavity.

7. Because of the permanence of thorotrast in the subarachnoid space, with the continuous opportunity for its radioactive destructive effect, the development of areas of fibrosis and cicatrices, the residence of the material in the proximity of the optic and other cranial nerves and the partial obstruction to absorption of the cerebrospinal fluid, with resultant hydrocephalus, we believe that the clinical application of thorotrast for encephalography and ventriculography is dangerous.

METABOLIC STUDIES DURING INSULIN HYPOGLYCEMIA THERAPY OF THE PSYCHOSES

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Dextrose has been considered by many investigators as the normal fuel for brain oxidation. It perhaps should be pointed out, however, that this is not the only substance which brain tissue can and does oxidize and that it is probable that there is more than one pathway for oxidation of carbohydrates.[1]

Since the discovery of insulin numerous articles have appeared describing various disturbances in the function of the central nervous system accompanying the production of hypoglycemia by injection of insulin.[2] These disturbances are usually readily relieved by the administration of dextrose. Dameshek and Myerson,[3] in 1935, and, recently, Himwich and his co-workers [4] have shown that the utilization of oxygen and dextrose by the brain is apparently markedly reduced during the hypoglycemic state. The latter investigators, in a recent article,[4] suggested that this reduction in oxidation and utilization of dextrose by the brain is the basis of the therapeutic effects of Sakel's treatment of dementia praecox by hypoglycemic shock.

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1. Gerard, R. W.: Metabolism of Brain and Nerve, in Luck, A. J.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6, p. 419.

2. Benedek, L.: Insulinshockwirkung auf die Wahrnehmung, Berlin, S. Karger, 1935. Wauchope, G. M.: Critical Review: Hypoglycemia, Quart. J. Med. **24**:117, 1933. von Angyal, L.: Ueber die verschiedenen Insulinshocktypen, Arch. f. Psychiat. **106**:663, 1937.

3. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: Mechanism of Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935.

4. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**: 271, 1937.

Hypoglycemia and reduction in oxidation and utilization of dextrose by the brain may be important factors in the mechanism whereby insulin produces its therapeutic effects. These changes, however, are not the only ones that occur in the metabolism of the organism under the influence of insulin. This has been pointed out by many investigators and will be evident from data which we shall present in this paper.

Many interesting clinical observations on patients with psychoses treated by induction of hypoglycemia indicate the complexity of the problem and the many questions which require elucidation.[5] A few may be enumerated. 1. The occurrence of a large percentage of unexplained failures. 2. The improvement shown by some psychotic patients before doses of insulin large enough to produce coma have been reached. 3. The sudden improvement in some patients following a convulsion during hypoglycemia. 4. The variety of neurologic manifestations in different patients during the hypoglycemic state. 5. The individual stereotyped nature of the neurologic manifestations exhibited constantly by certain patients, which calls to mind the characteristic electric brain waves possessed by each person, as reported recently. These neurologic differences in patients probably indicate fundamental differences in the constitution of the brain, which may be an important consideration in the effect of the therapeutic measures employed and the results obtained. 6. The differences in metabolic changes observed in various patients after the administration of insulin. We shall report on a study of some of these metabolic changes in patients with dementia praecox who were given hypoglycemic therapy.

PROCEDURE

The patients studied were all in the postabsorptive state. Venous blood from the basilic vein was obtained without stasis before administration of insulin and at intervals thereafter, until coma was interrupted by administration of dextrose. In some cases blood was obtained about one-half hour after administration of dextrose, when the patient had regained consciousness. Part of the blood was oxalated; the remainder was delivered under oil and the serum separated by centrifuging after the blood had been allowed to stand for one-half hour in the

5. Sakel, M.: Schizophreniebehandlung mittels Insulin-Hypoglykämie sowie hypoglykämischer Schocks, Wien. med. Wchnschr. **84**:1211, 1265, 1299, 1326, 1353 and 1401, 1934; **85**:35, 68, 94, 121, 152 and 179, 1935. Dussik, K. I., and Sakel, M.: Ergebnisse der Hypoglykämischeshockbehandlung der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:351, 1936. von Pap, Z.: Erfahrungen mit der Insulinshocktherapie bei Schizophrenen, Monatschr. f. Psychiat. u. Neurol. **94**:318, 1937. Müller, M.: Die Insulinschocktherapie der Schizophrenie, Schweiz. med. Wchnschr. **66**:929, 1936. Wilson, I. G. H.: A Study of Hypoglycemic Shock Treatment in Schizophrenia, London, His Majesty's Stationery Office, 1936.

ice box. Whole oxalated blood was examined for the following constituents: total reducing substances and fermentable reducing substances, which are generally assumed to be dextrose, amino-acid nitrogen and uric acid. The serum was analyzed for inorganic phosphorus, potassium, sodium, calcium, cholesterol and total protein. It was hoped in this way to obtain a more comprehensive picture of correlated metabolic changes taking place at various stages of the hypoglycemic state and thereby, perhaps, to disclose important physiologic differences in patients.

The dose of insulin varied for the different patients. It was the amount which had been found necessary for each person to produce the desired coma within approximately four hours. The lowest dose was 40 units, and the highest, 200 units.

OBSERVATIONS

It will be seen from tables 1 and 2 that the initial fasting level of the various constituents of the blood was normal for the entire group of patients investigated.

Blood Sugar.[6]—After administration of insulin there was a marked drop in the blood sugar in one hour, which within two hours had practically reached its lowest level for most patients. At this time all the patients were still conscious and usually showed only mild symptoms of hypoglycemia, such as sweating. Mental symptoms with stupor and coma appeared at some time after this, between two and four hours after administration of insulin. This is similar to the finding of Sakel that the dephth of coma bears no relation to the level of sugar in the peripheral venous blood. In fact, for some patients the blood sugar was slightly higher during the comatose period than at the end of the second hour (J. Q., R. L. and M. E., in table 1, and C. B., in table 2).[7]

Amino-Acid Nitrogen.[8]—The initial level of the amino-acid nitrogen of the blood ranged from 5.8 to 7.3 mg. per hundred cubic centimeters. The level declined steadily throughout the period of hypoglycemia. The drop amounted to from 15 to 26 per cent of the initial value. Only for one patient (R. K.) was the maximum drop slight, amounting to only 0.7 per cent. For half the patients the maximum drop during the hypoglycemic period was 20 per cent or more. Green[9] and his co-workers claimed that insulin has no effect on the level of amino-acid nitrogen. However, a number of investigators[10] have reported positive effects, such as those

6. Folin, O., and Wu, H.: Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367, 1920. Peters, J. P., and Van Slyke, D. D.: Determination of the Fermentable Sugar in Blood by Measuring the Decrease in Reducing Substances Caused by Yeast Fermentation, in Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 478.

7. The figures for the blood sugar given in the tables represent reducing substances fermentable by yeast.

8. Simonelli, U.: La determinazione spettrofotometrica degli amino-acidi del sangue, Riforma med. **50**:445, 1934.

9. Green, C. H.; Sandiford, K., and Ross, H.: Amino Acid Content of Blood in Normal and Pathologic Conditions, J. Biol. Chem. **58**:845, 1923.

10. (*a*) Luck, J. M.; Morrison, G., and Wilbur, L. F: Effect of Insulin on Amino Acid Content of Blood, J. Biol. Chem. **77**:151, 1928. (*b*) Daniels, A. C., and Luck, J. M.: Further Studies on the Effect of Insulin on the Amino

(Footnotes continued on page 120)

TABLE 1.—*Changes in the Blood During Insulin Hypoglycemia Treatment of Patients with Mental Disease*

Patient	Weight, Lb.	Dose of Insulin, Units	Time with Relation to Insulin	Blood Sugar, Mg. per 100 Cc.	Amino-Acid Nitrogen, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Sodium, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Serum Protein, Gm. per 100 Cc.	Comment
B. W.	143	70	Before	95	5.3	18.3	295	10.0	3.6	171	7.01	
			1 hour	37	4.9	18.3	299	10.0	3.3	175	6.93	
			2 hours	21	4.7	15.3	297	9.6	2.2	175	7.14	
			4 hours	18	4.4	17.8	...	....	3.5	190	7.96	Coma
			After ½ hour*	57	4.5	16.5	...	....	3.4	195	7.70	Awake
J. Q.	110	100	Before	91	5.9	19.2	299	10.4	3.3	224	6.40	
			1 hour	32	5.2	17.5	288	10.6	2.6	221	6.42	
			2 hours	17	5.0	18.7	300	9.5	2.4	225	6.57	
			4¾ hours	23	4.7	19.4	...	10.6	4.0	250	7.70	Coma
			After ¼ hour*	84	4.8	19.4	308	10.1	3.3	251	7.11	Awake
D. F.	150	85	Before	95	6.9	19.0	326	....	3.7	241	7.19	
			1 hour	24	6.6	17.7	...	....	3.4	241	7.19	
			2 hours	25	6.0	16.9	326	....	3.1	244	7.24	
			4½ hours	21	5.9	18.2	...	....	4.1	271	7.72	Stupor
M. Z.	141	65	Before	83	7.0	20.5	310	11.1	4.2	182	7.75	
			1 hour	34	5.8	17.7	310	11.0	3.4	181	7.55	
			2 hours	24	5.5	16.3	309	10.9	2.4	187	7.70	
			4½ hours	20	5.2	18.2	319	....	4.4	183	8.22	Coma
			After ½ hour*	68	4.8	20.4	325	10.9	5.5	185	8.22	Awake
R. L.	139	60	Before	84	6.7	19.2	317	9.8	3.0	159	6.58	
			1 hour	58	6.3	17.1	320	9.7	2.9	160	6.27	
			2 hours	24	5.8	16.4	320	10.0	2.2	176	6.73	
			5 hours	33	5.7	17.0	321	10.0	3.1	177	7.19	Stupor
			After ½ hour*	93	5.1	19.3	321	9.9	4.0	188	7.24	Awake
M. E.	123	200	Before	86	7.3	19.4	...	10.6	3.4	191	7.01	
			1 hour	37	6.9	17.1	...	10.8	2.3	173	6.93	
			2 hours	15	5.9	14.4	...	11.2	2.1	189	7.29	
			4 hours	21	5.6	17.6	...	11.2	3.4	...	....	Coma
R. K.	150	80	Before	80	5.8	17.9	...	10.2	4.3	278	7.58	
			1 hour	47	5.7	18.5	...	10.7	3.7	282	7.60	
			2 hours	18	5.4	....	...	....	...	...	....	
			4¼ hours	14	5.6	16.1	...	11.4	4.0	307	8.56	Coma

* Time after the administration of dextrose.

TABLE 2.—*Changes in the Blood of Patients Showing Marked Persistent Lowering of Serum Potassium During Hypoglycemia*

Patient	Weight, Lb.	Dose of Insulin, Units	Time with Relation to Insulin	Blood Sugar, Mg. per 100 Cc.	Amino-Acid Nitrogen, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Sodium, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Serum Protein, Gm. per 100 Cc.	Comment
B. H.	124	40	Before	82	7.1	19.8	...	11.0	3.4	...	....	
			1 hour	42	6.6	....	...	10.6	3.4	206	7.64	
			2 hours	20	6.4	14.7	...	10.9	2.3	...	7.88	
			4 hours	18	5.7	13.8	...	10.8	3.4	213	7.92	Coma
O. B.	115	90	Before	94	6.0	17.5	322	....	3.9	198	6.81	
			1 hour	55	5.9	....	...	....	...	...	....	
			2 hours	16	4.8	13.0	343	....	2.2	207	7.24	
			3½ hours	14	4.7	14.1	340	....	3.2	208	7.40	Coma
S. S.	119	115	Before	90	6.6	18.5	314	....	4.0	214	6.86	
			1 hour	22	6.4	15.9	328	....	3.6	219	6.77	
			2 hours	12	5.8	13.7	330	....	3.1	256	7.52	
			4 hours	18	5.4	13.9	319	....	4.1	250	7.62	Coma

observed for all but one of our patients. Davis and Van Winkle [10d] expressed the belief that the drop in the level of amino-acid nitrogen is due to the secretion of epinephrine, since in adrenalectomized animals injections of epinephrine, but not of insulin, produced this effect.

The amino-acid nitrogen was determined for four patients one-half hour after administration of dextrose, when they had regained consciousness. For two patients (B. W. and J. Q.) there was a slight rise of 0.1 mg. per hundred cubic centimeters, and for the other two (M. Z. and R. L.) there was a further drop of 0.4 mg. per hundred cubic centimeters. In spite of the further drop for the last two patients, the level reached was not quite as low as that observed for the first two patients during the period of hypoglycemia. In this connection, it is interesting to note that Slavich and Torrine [11] reported that the oral administration of 75 Gm. of dextrose produces a fall in the amino-acid nitrogen. It appears, therefore, that the level to which the amino-acids of the blood can be depressed may be limited and that when the decrease has occurred as a result of administration of insulin the ingestion of dextrose produces no further depression. This minimum level may be physiologically important.

Potassium.[12]—After administration of insulin there was a drop in potassium, which was greatest in the two hour period, except for patient J. Q., for whom the potassium reached its lowest level in one hour, and for patient B. H., for whom the potassium level was at its lowest in the four hour period. The maximum decrease in potassium varied from 11 to 35 per cent of the initial level, with a drop of over 20 per cent for the majority of patients. For three patients (B. H., C. B. and S. S., table 2), contrary to the findings for the other patients, the potassium persisted at a very low level at the four hour period. The potassium levels for these patients also dropped to the lowest for the entire group. The impression was gained that these patients reacted most severely to the hypoglycemia. This was not due to the dose of insulin used, since one patient (B. H.) received the smallest dose of insulin in the entire group, namely, 40 units.

Georgi,[13] who studied the changes in the potassium and calcium levels of the blood during therapeutic hypoglycemia, reported similarly that potassium falls during insulin hypoglycemia. He stated, however, that potassium is lowest during coma. In our group of patients, only a few showed such an effect as had previously been indicated, while the majority had the lowest level at the two hour period, while they were still conscious; the level of potassium then tended to rise during the four hour period, when the patients were in coma. Georgi did not give the actual figures, so that we could not make a comparison.

Acid Content of Blood, ibid. **91**:119, 1931. (*c*) Luck, L. M., and Morse, S. W.: Effect of Insulin and Adrenalin on the Amino Acid Content of Blood, Biochem. J. **27**:1648, 1933. (*d*) Davis, B. L., and Van Winkle, W.: Effect of Insulin and Epinephrine on the Amino Acid Content of the Blood of Adrenalectomized Rabbits, J. Biol. Chem. **104**:207, 1934. (*e*) Green, Sandiford and Ross.[9]

11. Slavich, E., and Torrine, A.: Modificazioni del livello aminoacidemico indotte da carico di glucosio in normoglicemici e diabetici, Boll. Soc. ital. di biol. sper. **11**:669, 1936; Nutrition Abstr. & Rev. **7**:110, 1937.

12. Breh, F., and Gaebler, O. H.: Determination of Potassium in Blood Serum, J. Biol. Chem. **87**:81, 1930.

13. Georgi, F.: Humoralpathologische Bemerkungen zur Insulinshocktherapie bei Schizophrenie, Schweiz. med. Wchnschr. **66**:935, 1936.

Inorganic Phosphorus.[14]—A marked drop in inorganic phosphorus occurred at the end of the two hour period and was followed by marked recovery in the four hour period. The decreases ranged from 20 to 44 per cent, and for the majority of patients were 30 per cent or more of the initial level. The significance of this decrease in phosphorus is not clear. Some investigators have suggested that it is due to the formation of phosphorylated compounds of hexose and other compounds by certain tissues, due to the action of insulin. Elias and Goldstein[15] expressed the belief that there is a shift of phosphorus to the nervous system, producing irritability of the cortex, the respiratory center and the peripheral nerves similar to that due to the injection of phosphates. However, our patients did not show such symptoms when the inorganic phosphorus level of the blood was at its lowest. It is possible, however, that the increase in inorganic phosphorus in the blood in the four hour period may have been derived from new sources.

Cholesterol.[16]—The total cholesterol was usually elevated in the four hour period, although for three patients (M. Z., B. H. and C. B.) the changes observed were slight. For the others the increases ranged from 18 to 42 mg. per hundred cubic centimeters. Georgi[13] stated that cholesterol rises and falls without relation

TABLE 3.—*Spontaneous Changes in the Blood of Patients Used as Controls Who Did Not Receive Insulin*

Patient	Time	Inorganic Phosphorus, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Amino-Acid Nitrogen, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Serum Protein, Mg. per 100 Cc.
R. W.	Preliminary	3.4	20.2	7.0	142	6.78
	2 hours	3.5	19.3	7.1	142	6.73
	4 hours	...	19.4	7.1	138	6.78
J. B	Preliminary	4.4	19.1	6.7	158	6.68
	2 hours	4.4	19.7	6.7	150	6.68
	4 hours	4.5	19.0	6.8	149	6.73
H. C.	Preliminary	3.8	19.0	6.7	228	7.08
	2 hours	3.8	18.9	6.7	232	7.08
	4 hours	3.8	17.8	6.6	230	7.08

to the other factors which he studied. In our patients the rise in cholesterol usually, but not always, accompanied the increase in serum protein.

Serum Protein.[17]—The serum protein, as determined by the refractive index, tended to increase from the two to the four hour period. This increase amounted to from 6 to 19 per cent. Some patients showed a slight or no change in level of serum protein during the first hour. There has been some controversy as to whether insulin hypoglycemia is accompanied by hydremia or by anhydremia.[18] In

14. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

15. Elias, H., and Goldstein, J.: Insulinshock und Zentralnervensystem, Med. Klin. **28**:542, 1932.

16. Schoenheimer, R., and Sperry, W. M.: Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.

17. Rostock, P.: Das Refraktometer in klinischen Laboratorium, Jap. Deutsche Ztschr. **1**:100, 1929.

18. Drabkin, D. L., and Edwards, D. J.: Production of Anhydremia with Insulin, Am. J. Physiol. **70**:273, 1924. Haldane, J. B. S.; Kay, H. D., and Smith, W.: Effect of Insulin on Blood Volume, J. Physiol. **59**:193, 1924. Hamilton, W. F.; Barbour, H. G., and Warner, J. H.: Does Insulin Significantly Affect Blood Concentration? J. Pharmacol. & Exper. Therap. **24**:335, 1924.

our patients, if one may judge from the changes in the refractive index of the serum, there was no change or slight hydremia in the first hour, and anhydremia then increased in the two and four hour periods.

Sodium [19] and *Calcium* [20].—With an occasional exception, sodium and calcium did not show any marked changes.

Table 3 shows the extent of the changes in various constituents of the blood for a group of three patients who did not receive insulin and thus served as controls.

COMMENT

It is obvious from the data presented that there is a marked disturbance in the interior milieu of the body during insulin hypoglycemia, affecting both organic and inorganic constituents. Many of these constituents are known to play important roles in the proper functioning of the central nervous system and other tissues.

A detailed consideration of the various constituents investigated and their interrelationship would involve too extensive a field of brain and tissue metabolism to be included in this paper. It may be desirable, however, to point out specifically some possibilities in the changes observed in functions of the central nervous system.

As regards the relationships of potassium and calcium, many important possibilities present themselves. Demole [21] and Cloëtta and his co-workers [22] reported that injection of a solution of calcium salts in the region of the tuber cinereum produces sleep, from which the animal can be aroused by injection of a solution of potassium salt. Gerard [23] stated that animals which have been narcotized by certain drugs can be aroused by the intravenous injection of a solution of potassium chloride. Ashford and Dixon [24] and Dickens and Greville [25] showed

19. Butler, A. M., and Tuthill, E.: Application of the Uranyl Zinc Acetate Method for the Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171, 1933.

20. Peters, J. P., and Van Slyke, D. D.: Modified Method of Halverson and Bergeim for the Determination of Small Amounts of Calcium Particularly in the Blood, in Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 767.

21. Demole, V.: Pharmakologisch-anatomische Untersuchungen zur Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

22. Cloëtta, M.; Fischer, H., and van der Loeff, M. R.: Die Biochemie von Schlaf und Erregung mit besonderer Berücksichtigung der Bedeutung der Kationen, Arch. f. exper. Path. u. Pharmakol. **174**:589, 1934. Cloëtta, M., and Fischer, H.: Ueber die Wirkung der Kationen Ca, Mg, Sr, Ba, K, und Na bei intrazerebraler Injektion, ibid. **158**:254, 1930.

23. Gerard, R. W.: Metabolism and Excitation, Cold Spring Harbor Symp., Quant. Biol. **4**:194, 1937; Factors Controlling Brain Potentials, ibid. **4**:292, 1937.

24. Ashford, C. A., and Dixon, K. C.: Effect of Potassium on Glycolysis in Brain Tissue, Biochem. J. **29**:157, 1935. Dixon, K. C.: Carbohydrate Catabolism in the Cerebral Cortex, ibid. **30**:1479, 1936. Dixon, K. C., and Holmes, E.:

(Footnote continued on next page)

by studies of brain tissue in vitro that the Pasteur effect, or the depression of carbohydrate metabolism under aerobic as compared with anaerobic conditions, can be inhibited by the addition of potassium salts.

Recent experiments have shown also that the action of salts is intimately related to neurohumeral mechanisms—for example, the role of potassium in the liberation and action of acetylcholine.[26]

It is obvious from these few citations from an extensive literature on the physiologic relationships of inorganic constituents that the marked changes in potassium and phosphorus and the disturbance in the ratio of potassium to calcium may play important roles in hypoglycemic treatment.

The failure of the markedly depressed level of potassium to recover in some cases may also indicate a disturbance in the nervous and humoral mechanisms. It has been shown recently by D'Silva [27] and Houssay and his co-workers [28] that epinephrine or stimulation of the splanchnic nerves liberates potassium, especially from the liver.

With respect to amino-acid metabolism, it has recently been shown that l-glutamic acid doubles the oxygen consumption of brain tissue in vitro.[1] It has been suggested that glutamic acid plays an important part as an ammonia carrier in cellular reactions, through the action of an enzyme, glutaminase, which is present in the brain in large amounts. The marked and persistent drop in amino-acids in the blood during insulin hypoglycemia obviously may have an important effect on this mechanism. Experimental studies on the role of various salts and amino-acids in the hypoglycemic state are now under way.

SUMMARY

1. A study has been made of concomitant metabolic changes occurring during the hypoglycemic state in psychotic patients treated with insulin.

Mechanism of the Pasteur Effect, Nature, London **135**:995, 1935. Dixon, K. C.: Inhibition of Pasteur Effect, ibid. **137**:742, 1936.

25. Dickens, F., and Greville, G. D.: Metabolism of Normal Tumor Tissue (Neutral Salt Effects), Biochem. J. **29**:1468, 1935.

26. Vogt, M.: Potassium Changes in the Stimulated Superior Cervical Ganglion, J. Physiol. **86**:258, 1936. Brown, G. L., and Feldberg, W.: Action of Potassium on the Superior Cervical Ganglion of the Cat, ibid. **86**:290, 1936.

27. D'Silva, J. L.: Action of Adrenalin on Serum Potassium, J. Physiol. **86**: 219, 1936.

28. Houssay, B. A.; Marenzi, A. D., and Gerschman, R.: Mecanismo simpático-adrenalino-hepático y potasio sanguíneo, Rev. Soc. argent. de biol. **12**:434, 1936; abstracted, Endocrinology **21**:565, 1937; Potassium sanguin et mécanisme sympathique-adrénalino-hépatique, Compt. rend. Soc. de biol. **124**:383, 1937.

2. In addition to lowering of the blood sugar, changes were observed in amino-acids, potassium, inorganic phosphorus, cholesterol and serum protein.

3. The importance of some of these changes in the physiologic relations of the nervous system is discussed.

4. The possible significance of a marked and persistent lowering of serum potassium observed in a small group of patients is pointed out.

5. The severity of the changes was not dependent on the size of the dose of insulin administered.

6. Plans for further experiments are indicated.

SPECIAL ARTICLE

EFFECTS OF HYPOGLYCEMIA AND ANOXIA ON THE CENTRAL NERVOUS SYSTEM

A BASIS FOR A RATIONAL THERAPY OF SCHIZOPHRENIA

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During the past three years a series of investigations has been carried out on man and animals in order to clarify the mechanism by which hypoglycemia acts on the central nervous system. These investigations seem to be of considerable practical importance, since insulin is used with some success in the treatment of schizophrenia. The purpose of the present paper is threefold: (1) to show that under the influence of hypoglycemia the central nervous system reacts in a manner similar to that observed in a state of anoxia and that hypoglycemia sensitizes the central nervous system to anoxia; (2) to discuss in the light of these findings the probable nature of the procedures commonly used in the treatment of schizophrenia, and (3) to suggest, on the basis of the experimental findings and the critical discussions, a new treatment for schizophrenia.

EFFECT OF HYPOGLYCEMIA ON THE CENTRAL NERVOUS SYSTEM

Olmsted and Logan [1] and Kleitman and Magnus [2] emphasized the similarity between the syndrome of anoxia and that of hypoglycemia as far as the central nervous system is concerned. Olmsted and Taylor [3] expressed the opinion that the similarity in the clinical pictures in the two conditions suggests similar disturbances in the brain; that is, that the fall in the sugar content of the blood causes depression of oxidative processes in the brain cells to such a degree that the effects are similar

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From the Department of Physiology and the Psychiatric Institute, University of Illinois College of Medicine.

1. Olmsted, J. M. D., and Logan, H. D.: The Effect of Insulin on the Central Nervous System and Its Relation to the Pituitary Body, Am. J. Physiol. **66**:437, 1923.

2. Kleitman, N., and Magnus, R.: Zur Wirkung des Insulins auf das Zentralnervensystem, Arch. f. d. ges. Physiol. **205**:148, 1924.

3. Olmsted, J. M. D., and Taylor, A. C.: The Effect of Insulin on the Blood: I. Changes in Oxygen Saturation, Percentage Hemoglobin and Oxygen Capacity, Am. J. Physiol. **69**:142, 1924.

to those of anoxia produced by the inhalation of gas mixtures poor in oxygen. However, although Olmsted and Taylor noted a fall in the oxygen saturation of the blood after convulsions induced by insulin, Kleitman and Magnus stated that convulsions due to hypoglycemia occurred even in experiments with artificial respiration. These observations did not prove anything either for or against the theory that the oxidative metabolism of the brain is diminished as a result of the effects of insulin on the central nervous system, since the changes in oxygen saturation may be due to secondary effects of the convulsions (interference with respiration and greatly increased muscular activity), but they were important stages in the development of the theory that the oxidative metabolism of the brain is diminished in hypoglycemia. An exact basis for this theory was given in the experiments by Holmes [4] and Wortis,[5] who found that the oxygen consumption of sliced brain tissue parallels the concentration of dextrose in the medium and that the oxygen consumption of brain tissue obtained from an insulinized animal is lower than that of brain tissue from animals used as controls. The application of these findings to the intact organism was made by Dameshek and Myerson,[6] who showed in the human subject a decrease in the difference between arterial and venous blood with respect to the oxygen and dextrose contents (the venous blood was taken from the internal jugular vein). Similar results were those obtained by Himwich and his collaborators.[7] A decrease in the difference between the oxygen content of arterial and that of venous blood proves the diminished oxygen uptake of an organ only if the blood flow is not increased. Sufficient data on this cardinal point are lacking, but Loman and Myerson [8] stated that in several subjects they found a slight decrease in blood flow through the brain, thereby supporting the theory that hypoglycemia of the central nervous system is accompanied by a decreased rate of oxidation.

Recent experiments by Gellhorn [9] and Yesinick have thrown new light on this problem. They studied the effects of increased intracranial

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4. Holmes, E.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

5. Wortis, S. B.: Respiratory Metabolism of Excised Brain Tissue: II. The Effects of Some Drugs on Brain Oxidations, Arch. Neurol. & Psychiat. **33**:1022 (May) 1935.

6. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: The Mechanism of Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935.

7. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**:271, 1937.

8. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Cranio-Vertebral Cavity, Am. J. Psychiat. **92**:791, 1936.

9. Gellhorn, E., and Yesinick, L.: Studies on the Effect of Increased Intracranial Pressure, Proc. Am. Physiol. Soc., 1938, p. 76.

pressure on the blood pressure of narcotized dogs subjected to pneumothorax and artificial respiration under conditions of oxygen deficiency and insulin hypoglycemia. They used a reaction studied by Cushing,[10] who showed that when the intracranial pressure is equal to or greater than the mean a rise in blood pressure occurs during the period of increased intracranial pressure. If the intracranial pressure is raised to the level of the blood pressure, the reaction is constant on frequent repetition. Therefore, the influence of inhalation of from 7 to 9 per cent oxygen and that of insulin hypoglycemia on the brain were tested by increasing the intracranial pressure. As table 1 indicates, the rise in blood pressure following increase in intracranial pressure is much greater than normal

TABLE 1.—*Reaction of the Blood Pressure to Increase in Intracranial Pressure*

I. Influence of Anorexia

Gas Mixture Inhaled	Blood Pressure, Mm. of Mercury	Intracranial Pressure, Mm. of Mercury	Difference in Blood Pressure and Intracranial Pressure, Mm. of Mercury	Response of Blood Pressure, Mm. of Mercury
Air	105	100	5	+28
7.8 per cent oxygen	116	112	4	+46
Air	119	115	4	+28

II. Influence of Hypoglycemia

Time	Response of Blood Pressure to Increased Intracranial Pressure*	Blood Sugar, Mg. per 100 Cc.	Comment
10:30 a.m.	14	119	Control
10:33 a.m.	..	...	Insulin
12:13 p.m.	20	84	
12:26 p.m.	46	63	
2:00 p.m.	52	49	
3:00 p.m.	..	...	Dextrose injected intravenously
3:15 p.m.	17	137	

* The difference between the blood pressure and the increased intracranial pressure was 0 throughout the experiment.

during a period either of hypoglycemia or of oxygen deficiency. The initial conditions may be restored by injection of dextrose or inhalation of air, respectively.

The experiments of Gellhorn and Yesinick make it probable that the Cushing reaction is due not to the effect of pressure on the nerve tissue but to the interference of the pressure with the circulation in the brain. When the intracranial blood pressure is raised to or above the level of the blood pressure, the circulation in the brain, particularly in the medulla, is impeded or stopped. Asphyxia of the medullary centers stimulates the sympathetic centers and a rise in blood pressure

10. Cushing, H.: Concerning a Definite Mechanism of the Vasomotor Center Which Controls Blood Pressure During Cerebral Compression, Bull. Johns Hopkins Hosp. **12**:290, 1901.

results. When, however, a certain degree of anoxia is already established by inhalation of a gas mixture low in oxygen, a given rise in intracranial pressure will effect marked total asphyxia and greater excitation of the sympathetic centers than when the stimulus is applied to the normally oxygenated brain. The rise in blood pressure is therefore greater than under the conditions serving as a control.

The fact that in this instance hypoglycemia has an effect similar to that of inhalation of a gas mixture poor in oxygen becomes understandable on the basis of the anoxidation theory of hypoglycemia. If, as the investigations of Holmes,[4] Wortis,[5] Dameshek and Myerson,[6] Loman and Myerson [8] and Himwich and his collaborators [7] suggest, lowering the blood sugar reduces the oxygen consumption of the brain, oxidation in this organ is lowered when the supply of either oxygen or dextrose is reduced. It is important to note that this reasoning does not apply to other organs in a similar degree, since the heart, for instance, can metabolize proteins and fat whereas the respiratory quotient of the brain is almost equal to 1 (Himwich and Nahum,[11] Dickens and Simer [12] and Lennox [13]). This indicates the rather exclusive consumption of carbohydrates in the brain.

The similarity of the effects of hypoglycemia and those of oxygen deficiency produced by inhalation of gas mixtures poor in oxygen made it seem probable that the organism in a state of hypoglycemia becomes more sensitive to anoxia. This hypothesis was tested in the experiments by Glickman and Gellhorn.[14] They injected insulin into rats under standard conditions and determined the time that elapsed before the onset of convulsions. As soon as these occurred the rats were given sufficient dextrose by intraperitoneal injection to permit recovery. After five days the same experiment was repeated with the following modification: After the injection of insulin the rats were placed in a low pressure chamber and kept at a pressure of 460 mm. of mercury for two hours. Experiments made as controls showed that the anoxia produced in this chamber did not harm normal rats even when the time of exposure was much longer than in the experiments cited. Nevertheless, it was found that in 80 per cent of the rats the latent period of the insulin convulsions was greatly shortened in the low pressure experiments. Moreover, a considerable number of rats died in the latter

11. Himwich, H. E., and Nahum, L. H.: The Respiratory Quotient of the Brain, Am. J. Physiol. **101**:466, 1932.

12. Dickens, F., and Simer, F.: The Metabolism of Normal and Tumor Tissue: IV. The Respiratory Quotient in Bicarbonate Media, Biochem. J. **25**:985, 1931.

13. Lennox, W. G.: Cerebral Circulation: The Respiratory Quotient of the Brain and of the Extremities in Man, Arch. Neurol. & Psychiat. **20**:719 (Oct.) 1931.

14. Glickman, N., and Gellhorn, E.: The Effect of Oxygen Deficiency on the Sensitivity of Rats to Insulin, Am. J. Physiol. **121**:358, 1938.

experiments in spite of the injection of dextrose. Those which survived were again given injections of insulin under conditions serving as a control. The latent period was again similar to that obtained in the first control experiment. These experiments show clearly that hypoglycemia sensitizes the animals to anoxia. It is important to note that the clinical picture of the insulin convulsions obtained in the low pressure chamber was somewhat different from that observed at atmospheric pressure and resembled in all details convulsions resulting from anoxia which may be produced by lowering the pressure in the chamber below a critical level.

In order to interpret these results correctly, it is necessary to know the course of the blood sugar curves obtained after the injection of insulin under conditions serving as a control and in a chamber at a pressure of 460 mm. of mercury. First, it was found that exposure of the rats to a pressure of 460 mm. of mercury for one hour did not affect the blood sugar level. Then an injection of insulin was given, and the blood sugar was determined one hour later. This experiment was repeated in five days while the animal was exposed to an atmospheric pressure of 460 mm. of mercury for one hour, and five days later the control experiment (injection of insulin at normal atmospheric pressure) was again carried out. The experiments showed that the blood sugar in the insulin–low pressure experiment was even slightly higher than in the preceding and subsequent experiments made as controls, in which insulin alone was given. From this it follows that rats show increased sensitivity to oxygen deficiency in insulin hypoglycemia, although the blood sugar level is not lower, but even slightly higher, than that in rats given insulin and exposed to atmospheric pressure. This result is easily understood on the basis of the theory that insulin hypoglycemia reduces the oxidative metabolism of the brain. It means merely that if the rate of oxidation is lowered a further reduction in the oxidative processes may become critical. It is immaterial, however, whether a decrease in the oxygen tension of the blood or a decrease in the level of the blood sugar is chosen. In either case the oxidative processes of the brain are reduced.

The important question as to the changes in the central nervous system resulting from the combined administration of insulin and oxygen deficiency was investigated in the following experiments (Moldavsky and Gellhorn [15] and Ingraham, Moldavsky and Gellhorn [16]).

15. Moldavsky, L., and Gellhorn, E.: On the Relation Between Hypoglycemia and Anoxemia, Proc. Soc. Exper. Biol. & Med. **36**:92, 1937.

16. Ingraham, R. C.; Moldavsky, L., and Gellhorn, E.: On the Relation Between Hypoglycemia and Anoxemia, Am. J. Physiol. **119**:341, 1937. Gellhorn, E.; Ingraham, R. C., and Moldavsky, L.: The Influence of Hypoglycemia on the Sensitivity of the Central Nervous System to Oxygen Want, J. Neurophysiol., July 1938, to be published.

It is known that the normal narcotized dog shows a rise in blood pressure on inhalation of gas mixtures poor in oxygen, which is due to reflex stimulation of the vasomotor center through the chemoreceptors in the carotid sinus and the aorta (Lambert and Gellhorn [17]). The way in which this response of the blood pressure to oxygen deficiency is altered when the blood sugar is lowered by injections of insulin has now been studied. Numerous experiments on dogs narcotized with amytal, soluble barbital U. S. P. (sodium barbital), a mixture of chloral and dextrose (chloralose) or chloralosane have shown uniformly that the rise in blood pressure resulting from the inhalation of 6.2 per cent oxygen for from one to three minutes increases with the decrease in blood sugar. Since the rise in blood pressure resulting from the

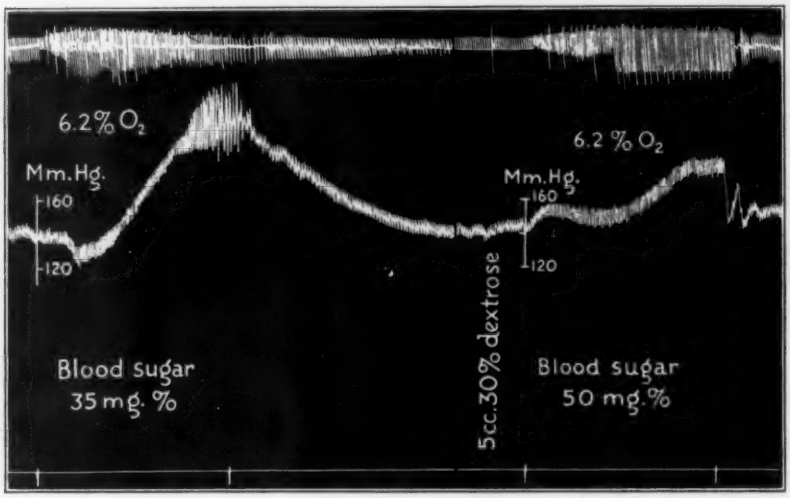

Fig. 1.—Influence of the level of the blood sugar on the reaction of the blood pressure to inhalation of 6.2 per cent oxygen in a dog under soluble barbital U. S. P. (sodium barbital) anesthesia. Records for respiration and blood pressure are shown. The marks indicate inhalation of 6.2 per cent oxygen for three minutes. "Mg. %" means milligrams per hundred cubic centimeters.

inhalation of gas mixtures poor in oxygen increases also with decrease in the concentration of the oxygen which is inhaled, the experiments show again that in the state of hypoglycemia the sensitivity of the central nervous system to oxygen deficiency is increased. Figure 1 shows not only the tremendous response of the blood pressure to inhalation of 6.2 per cent oxygen when the blood sugar is at a low level (35 mg. per hundred cubic centimeters) but a great reduction in the response when through intravenous administration of dextrose the level of the blood

17. Lambert, E., and Gellhorn, E.: The Role of Afferent Nerves in the Response of the Vasomotor Center to Oxygen Deficiency, Proc. Soc. Exper. Biol. & Med. **38**:427, 1938.

sugar is partially restored. Experiments of this kind showed the specific significance of dextrose for the brain, since other sugars, such as levulose, only partially restored the original reaction of the vasomotor center and galactose was entirely without effect.

Both groups of experiments, those on rats in which insulin convulsions were precipitated by lowering the barometric pressure and those on narcotized dogs in which the response of the blood pressure to inhalation of oxygen in low concentration is greatly increased, are interpreted to mean that hypoglycemia produces, by reduction in the oxidation of dextrose, a state of lowered oxidative metabolism in the brain. If this hypothesis is correct, other signs comparable with those of anoxia of the central nervous system are to be expected. This is, in fact, the case. Figure 2 shows that inhalation of 6.2 per cent oxygen when the sugar content of the blood is 72 mg. per hundred cubic

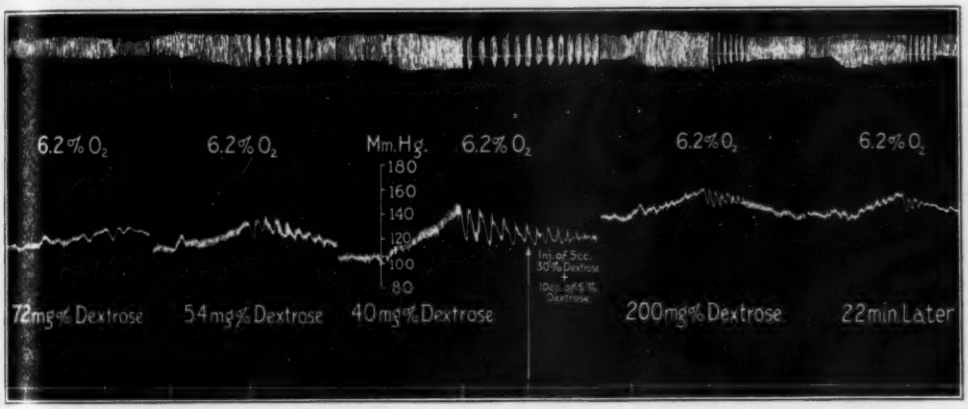

Fig. 2.—Records for respiration and blood pressure showing the development and disappearance of the Cheyne-Stokes breathing during hypoglycemia. The marks indicate inhalation of 6.2 per cent oxygen for three minutes. The dextrose values refer to the blood sugar concentrations, expressed in milligrams per hundred cubic centimeters.

centimeters does not produce any irregularities in respiration, whereas the same test results in prolonged Cheyne-Stokes rhythms after the level of the blood sugar is lowered. This phenomenon occurs on readmission of air. Reestablishment of the dextrose level restores either in part or completely the original reaction. Similar effects on respiration may be seen after prolonged periods of breathing gas mixtures low in oxygen.

The increase in blood pressure in response to low concentrations of oxygen in cases of hypoglycemia must be attributed to increased sympathetic discharges. The question arises whether, under these circumstances, an increased discharge from the adrenal glands is

involved. The experiments which Ingraham and I [18] have carried out thus far seem to indicate that, at least in dogs with chloralosane anesthesia, the adrenal glands are not involved, since ligation of the adrenal veins does not alter the increased response in blood pressure to oxygen deficiency in the state of hypoglycemia. The question, however, is not settled by these experiments, since Kettenmeyer and La Barre [19] showed that the secretion of epinephrine after injection of insulin is absent after the administration of various narcotic drugs and seems to depend on the excitability of thalamic centers. It is probable that under suitable conditions the increased sympathetic discharge may also lead to an increased release of epinephrine from the adrenal glands.

Another study which is of importance to the theory that the oxidative metabolism of the brain is diminished in hypoglycemia may be reported briefly. It consists of experiments in which the effect of hypoglycemia on the tension of carbon dioxide in the alveolar air and in the arterial blood was investigated. These investigations were based on the following considerations. It is well known that in the intact organism the respiratory volume is greatly increased on inhalation of gas mixtures deficient in oxygen. If hypoglycemia and oxygen deficiency affect nerve structures in a similar manner, hyperventilation should result in either condition. Since more carbon dioxide is exhaled as a result of hyperventilation, a fall in the carbon dioxide tension of alveolar air similar to that which is a constant finding in men and animals exposed to low oxygen tension would be expected in subjects with hypoglycemia. Experiments were carried out by Domm and Gellhorn [20] on patients with schizophrenia who were subjected to the insulin treatment.[21] Table 2 illustrates some results. The alveolar air was collected automatically by means of the method of Henderson and Haggard.[22] Although the values were considerably lower than those obtained in experiments carried out as controls on normal persons and the values obtained as controls from these patients on various days prior to the injection of insulin differed considerably, two facts stand out.

1. With a decrease in the blood sugar the carbon dioxide tension of the alveolar air decreases.

2. On administration of dextrose during the state of hypoglycemia the carbon dioxide tension of the alveolar air rises. This rise leads

18. Ingraham, R. C., and Gellhorn, E.: Unpublished experiments.

19. Kettenmeyer, G., and La Barre, J.: The Effect of Paralysis of the Thalamic Centers on Adrenaline Secretion, J. Physiol. **90**:13P, 1937.

20. Domm, S., and Gellhorn, E.: Unpublished observations.

21. The experiments were carried out in the Psychiatric Institute of the University of Illinois College of Medicine. Prof. H. D. Singer and the staff cooperated in the study.

22. Henderson, Y., and Haggard, H. W.: The Circulation and Its Measurement, Am. J. Physiol. **73**:193, 1925.

in general to values even higher than those obtained during the control experiment prior to the injection of insulin.

It may therefore again be said that the effect of hypoglycemia is similar to that of oxygen deficiency in that each condition causes a fall in the tension of carbon dioxide in the alveolar air and that administration of dextrose during hypoglycemia restores the conditions of the control experiment, as does the inhalation of air after a period of anoxia.

Similar experiments were carried out on dogs in which the experimental conditions could be controlled more rigidly. Light morphine anesthesia was used; the femoral artery and vein were exposed with the use of local anesthesia, and after time sufficient to bring about slow,

TABLE 2.—*Carbon Dioxide Tension in Alveolar Air and Sugar Content of the Blood in Schizophrenic Patients During Insulin Treatment*

No. of Experiment	Tension in Carbon Dioxide Alveolar Air, Percentage	Blood Sugar, Mg. per 100 Cc.
19	3.85	110.5
	3.48	44.1
	3.52	46.0
After sucrose	4.44	117.0
21	4.58	115.0
	4.19	47.5
After sucrose	5.07	109.0
13	3.83	105.2
	2.82	37.5
	2.34	35.3
16	3.77	130.0
	3.84	90.0
	3.48	57.3
After sucrose	4.10	98.2
9	4.38	85.3
	3.10	25.7

regular respiration had elapsed insulin was injected intravenously. At suitable intervals the total carbon dioxide content, the *p*H and the sugar content of the arterial blood were determined, and the carbon dioxide tension of the arterial blood was obtained from Van Slyke's nomogram.[23] A typical experiment (fig. 3) shows that in association with hypoglycemia the carbon dioxide tension of the arterial blood falls and that on administration of dextrose it rises again, although the two curves are not strictly parallel. Since the carbon dioxide tension of the arterial blood is in equilibrium with that of the alveolar air, the carbon dioxide tension curve for arterial blood was expected to be similar to that for alveolar air. The experiments show that this is the case under conditions of hypoglycemia in man and animals.

23. Van Slyke, D. D., and Sendroy, J., Jr.: Studies of Gas and Electrolyte Equilibria in Blood: XV. Line Charts for Graphic Calculation, J. Biol. Chem. **79**:781, 1928.

The experiments just described present four lines of evidence in favor of the hypothesis that hypoglycemia and anoxia act on the central nervous system in a similar manner. They also show that the combination of hypoglycemia and anoxia leads to effective stimulation of the sympathetic nervous system. Since it has been shown that all effects described thus far are dependent on the level of the blood sugar and not on the amount of insulin injected, the observations make it probable that the curative effect of hypoglycemia in the treatment of schizophrenia is based on the anoxidative effect on the central nervous system and is closely linked with the excitation of the sympathetic division of the autonomic system.

This interpretation is supported by clinical observations on the effect of hypoglycemia in man. Cortical functions, particularly the highest,

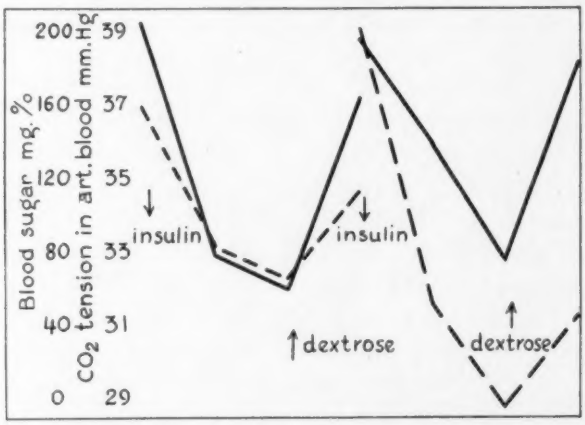

Fig. 3.—Carbon dioxide tension and sugar content of arterial blood of morphinized dogs. The solid line indicates the blood sugar, expressed in milligrams per hundred cubic centimeters, and the dotted line, the carbon dioxide tension of the arterial blood. The arrow indicates the intravenous injection of dextrose.

such as association, memory and the performance of simple mental operations, as for instance, the addition of digits (Kraepelin's test) and the crossing out of a letter from a printed page (Bourdon's test), are impaired during hypoglycemia (Wiedeking [24]) as well as during anoxia (Gellhorn,[25] Gellhorn and Kraines [26] and Gellhorn and Joslyn [27]).

24. Wiedeking Jr.: Selbstbeobachtungen im hypoglykämischen Zustand, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:417, 1937.

25. Gellhorn, E.: The Influence of Carbon Dioxide in Combating the Effect of Oxygen Deficiency on Psychic Processes, Am. J. Psychiat. **93**:1413, 1937.

26. Gellhorn, E., and Kraines, S. H.: Word Associations as Affected by Deficient Oxygen, Excess of Carbon Dioxide and Hyperpnea, Arch. Neurol. & Psychiat. **38**:491 (Sept.) 1937.

27. Gellhorn, E., and Joslyn, A.: The Influence of Oxygen Want, Hyperpnea and Carbon Dioxide Excess on Psychic Processes, J. Psychol. **3**:161, 1936.

Cutaneous sensory functions are impaired even in patients with moderate degrees of hypoglycemia (Achelis [28]). This is again in agreement with observations by Gellhorn and Spiesman,[29] Gellhorn,[30] McFarland,[31] Berger and Bøje [32] and Hartmann [33] on the reduction of visual, auditory and tactile functions under conditions of anoxia.

The not infrequent occurrence of the Cheyne-Stokes breathing in association with hypoglycemia in man (Beiglböck and Dussik [34]) gives further support to my interpretation. Of interest is the fact that hypoglycemia in man is associated with a considerable fall in body temperature, since a similar reaction was observed in the low pressure chamber by Béhague, Garsaux and Richet; [35] Chevillard and Mayer,[36] and Cordier and Mayer.[37] Gellhorn and Janus [38] showed that the reaction depends on the oxygen tension of the inhaled air. The biologic importance of the response is great, since the reduction in body temperature diminishes the oxygen requirement of the organism to such a degree that an animal may tolerate a certain low oxygen concentration which is regularly fatal when the temperature-lowering reaction is prevented

28. Achelis, J. D.: Die Physiologie der Schmerzen, Nervenarzt **9**:559, 1936.

29. Gellhorn, E., and Spiesman, I.: The Influence of Hyperpnea and of Variations of O_2- and CO_2-Tension in the Inspired Air upon Hearing, Am. J. Physiol. **112**:519, 1935; The Influence of Hyperpnea and of Variations of the O_2- and CO_2-Tension in the Inspired Air upon After-Images, ibid. **112**:620, 1935.

30. Gellhorn, E.: The Effect of O_2-Lack, Variations in the CO_2-Content of the Inspired Air, and Hyperpnea on Visual Intensity Discrimination, Am. J. Physiol. **115**:679, 1936; The Effectiveness of Carbon Dioxide in Combating the Changes in Visual Intensity Discrimination Produced by Oxygen Deficiency, ibid. **117**:75, 1936.

31. McFarland, R. A.: Psycho-Physiological Studies at High Altitude in the Andes, J. Comp. Physiol. **23**:191 and 227, 1937; **24**:147 and 189, 1937.

32. Berger, C., and Bøje, O.: Ueber den Einfluss von Sauerstoffmangel auf das Auflösungsvermögen des emmetropen Auges, Skandinav. Arch. f. Physiol. **77**:129, 1937.

33. Hartmann, H.: Die Wirkung grosser Höhen auf den Organismus vor und nach erfolgter Anpassung, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **47**:48, 1935.

34. Beiglböck, W., and Dussik, K. T.: Zur Physiologie des hypoglykämischen Schocks bei der Behandlung der Schizophrenie, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:38, 1937.

35. Béhague, P.; Garsaux, and Richet, C., Jr.: Modifications thermiques observées sur lapin: Soumis à la depression atmosphérique, Compt. rend. Soc. de biol. **96**:766, 1927.

36. Chevillard, L., and Mayer, A.: Influence de la tension de l'oxygène contenu dans l'air inspiré sur les échanges gazeux de la souris, Ann. de physiol. **11**:225, 1935.

37. Cordier, D., and Mayer, A.: Influence de la tension de l'oxygène contenu dans l'air inspiré sur la consommation d'oxygène des mammifères: Étude sur le chien, Ann. de physiol. **11**:199, 1935.

38. Gellhorn, E., and Janus, A.: The Influence of Partial Pressure of Oxygen on Body Temperature, Am. J. Physiol. **116**:327, 1936.

(Gellhorn [39]). Whether the reduction of body temperature associated with hypoglycemia has a similar biologic significance is under investigation at present.

Histologic investigation of the brains of patients and animals (Moersch and Kernohan,[40] Bodechtel,[41] Wohlwill,[42] Terplan [43] and Weil and his collaborators [44]) subjected to large amounts of insulin frequently offer a picture which strongly resembles the degenerative changes in ganglion cells observed after anoxia (Gildea and Cobb [45]) and after nitrogen monoxide poisoning (Courville [46]).

It may therefore be stated that experimental and clinical observations make it almost certain that hypoglycemia produces a reduced rate of oxidation in the central nervous system. That this stimulates the sympatheticoadrenal system is evident clinically from the not infrequent dilatation of the pupils and exophthalmos (von Pap [47]), rise in blood pressure and the profound sweat secretion commonly observed.

Two facts stand out: 1. The hypoglycemia treatment of schizophrenia has been successful in a considerable number of cases. 2. The experimental and clinical evidence presented in this paper substantiates the theory that the beneficial effect is based on the development of a reduced rate of oxidation in the brain with subsequent stimulation of the sympathetic division of the autonomic nervous system.

PHYSIOLOGIC CRITICISM OF THE THEORIES UNDERLYING THE THERAPY OF SCHIZOPHRENIA

These findings make it advisable to consider in the light of the preceding discussions the various therapeutic procedures for which some

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39. Gellhorn, E.: Oxygen-Deficiency, Carbon Dioxide and Temperature Regulation, Am. J. Physiol. **120**:190, 1937.

40. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat. **39**:242 (Feb.) 1938.

41. Bodechtel, G.: Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, zugleich ein Beitrag zu seiner Pathogenese, Deutsches Arch. f. klin. Med. **175**:188, 1933.

42. Wohlwill, F.: Ueber Hirnbefunde bei Insulin-Ueberdosierung, Klin. Wchnschr. **7**:344, 1928.

43. Terplan, K.: Changes in the Brain in a Case of Fatal Insulin Shock, Arch. Path. **14**:131 (July) 1932.

44. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938,

45. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

46. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129, 1936.

47. von Pap, Z.: Erfahrungen mit der Insulinshocktherapie, Monatschr. f. Psychiat. u. Neurol. **94**:318, 1937.

success is claimed in order to arrive at a reasonable view of the mechanisms involved. If this can be achieved, some light will be thrown on the disease process itself, at least as concerns the physiologic mechanism which is disturbed in schizophrenia.

First an accurate statement may be given of the theories held by the originators of the various therapeutic procedures concerning the mechanisms called into play. Sakel [48] expressed the belief that insulin causes blockage of cells.

> This condition of artificial rest of the cell results in little or no activity in all paths. Consequently, the pathologic paths fade first, whereas the normal paths, which are more deeply engraved, are allowed to recover and to be polarized.[49]

Obviously this "theory" does not deserve serious physiologic consideration, since it is based on concepts having no scientific foundation. It is not justified by any anatomic or physiologic principles but merely describes, by means of popular terms in which the central nervous system is compared with a telegraph system, the fact that a pathologic process ("disorganization of paths") is changed into a physiologic process (restoration of "normal paths").[50] More important is the view of von Pap,[47] who expressed the belief that the essential cause of the curative effects of insulin is linked not with the chemical and physiologic properties of insulin but with the elimination of consciousness in coma, particularly with *der Dissoziation der Bewusstseinsinhalte* (dissociation of mental content). Support for this idea is the fact that no therapeutic effects were observed with large protracted doses of insulin which did not lead to coma, but that success was obtained, even in the same patient, with smaller doses which led to coma. The greater effect of a smaller dose given once as compared with that of a total greater dose given in many small portions is understandable on physiologic grounds. If, as I assume, the hypoglycemia treatment is successful because it leads to excitation of the sympathetico-adrenal apparatus through hypoglycemia of the brain, many small single doses will have no effect because under these circumstances the level of the blood sugar is not lowered sufficiently to reduce the oxidation rate of the brain and to excite the sympathetic nervous system.

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48. Sakel, M.: Schizophreniebehandlung mittels Insulin-Hypoglykämie sowie hypoglykämischer Schocks, Wien. med. Wchnschr. **84**:1211, 1265, 1299, 1326, 1353, 1383 and 1401, 1934; **85**:35, 68, 94, 121, 152 and 179, 1935.

49. *Dieser Umstand der künstlichen Ruhe ermöglicht es der Zelle, durch gar keine oder verminderte Beanspruchung sämtlicher Bahnen, die pathologischen Bahnen zum Verblassen zu bringen und die normalen Bahnen als die eingefahreneren erholen zu lassen und zu polarisieren.*[48]

50. In his most recent discussion (Das Wesen und die Entstehung der Hypoglykämiebehandlung der Psychosen, Schweiz. Arch. f. Neurol. u. Psychiat. [supp.] **39**:83, 1937), Sakel has not given a more satisfactory explanation.

It may be appropriate to discuss here the possibility that the action of insulin is due to unknown effects of this substance which are not necessarily related to its influence on the level of the blood sugar. This idea must be refuted, on the following grounds. In numerous experiments on dogs I have found not infrequently that even large doses of insulin do not greatly affect the level of the blood sugar. When this was the case, the typical increased sensitivity to a low concentration of oxygen as measured by the response of the blood pressure was absent. Although the critical level of blood sugar at which the increased response to oxygen deficiency appears varies within wide limits in different animals and may be due to the variable depression of medullary centers produced by narcosis, it was found that the effect was not related to the dose of insulin but to the level of the blood sugar. The only other factor which is of importance is time, since the increased sensitivity to anoxia increases with time when the decreased concentration of sugar in the blood remains constant.

The interpretation which I have given to the effects of hypoglycemia on the central nervous system is fundamentally opposed to that of Wespi [51] and Pfister.[52] Both authors were aware of the vegetative effects of insulin hypoglycemia in patients with schizophrenia. Pfister expressed the belief that insulin has a dampening effect on the sympathetic nervous system, and Wespi was disappointed not to find indications of an increased "parasympathetic tone." These authors obviously confused the effect of increased endogenous secretion of insulin with that of insulin administered by injection. It is established that the secretion of insulin is partially regulated by the vagus nerve (Britton [53] and Geiger, Binder and Rusztek [54]), so that increased production of insulin may be considered as a sign of increased parasympathetic activity. The physiologic stimulus which brings about such parasympathetic activation is an increase in the amount of blood sugar in the brain (La Barre [55]). If, however, insulin is injected and the level of the blood sugar is lowered, the production of insulin in the organism is dimin-

51. Wespi, H.: Vorläufige Mitteilung über Beobachtungsresultate von vegetativen Funktionen bei der Insulinschockbehandlung Schizophrener, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:77, 1937.

52. Pfister, H. O.: Die neuro-vegetativen Störungen der Schizophrenien und ihre Beziehungen zur Insulin-, Cardiazol- und Schlafkurbehandlung, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:77, 1937.

53. Britton, S. W.: The Nervous Control of Insulin Secretion, Am. J. Physiol. **74**:291, 1925.

54. Geiger, E.; Binder, I., and Rusztek, A.: Ueber die Rolle des Vagus bei der Blutzuckerregulation, Arch. f. exper. Path. u. Pharmakol. **176**:355, 1934.

55. La Barre, J.: Intervention du système nerveux dans les troubles glycorégulateurs observés au cours du diabète pancréatique experimental, Bull. Acad. roy. de med. de Belgique **11**:304, 1931.

ished (Zunz and La Barre [56]), but the sympatheticoadrenal system is stimulated (Cannon [57] and Cannon, McIver and Bliss [58]). This reaction is similar to that obtained after exposure to a low concentration of oxygen (Kellaway [59] and Sawyer, Schlossberg and Bright [60]).

I shall now discuss briefly the *Dauerschlaf* treatment of schizophrenia. Aside from psychologic considerations, Kläsi [61] introduced this treatment mainly with the purpose of eliminating excitatory phenomena. However, a different interpretation of the procedure, based on the work of Quastel and Wheatley [62] and Jowett and Quastel,[63] can be given. These authors have shown that narcotics, especially the barbiturates, inhibit the oxidation of sliced brain tissue. It is important (1) that this inhibitory influence occurs in vitro in concentrations similar to those used in vivo to produce narcosis and (2) that this influence refers specifically to the oxidation of dextrose and intermediary products of carbohydrate metabolism.

These experiments establish a physiologic similarity between the insulin treatment and the prolonged narcosis therapy, of which Quastel [64] was fully aware. However, instead of attempting to interpret the narcosis therapy on physiologic grounds, he propounded a theory which is as far removed from sound physiologic and clinical facts as is Sakel's.[65] From my point of view, there is no difficulty in interpreting the effects

56. Zunz, E., and La Barre, J.: Contributions à l'étude des variations physiologiques de la sécrétion interne du pancreas, Arch. internat. de physiol. **31**:1, 1929.

57. Cannon, W. B.: The Wisdom of the Body, New York, W. W. Norton, 1932.

58. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

59. Kellaway, C. H.: The Hyperglycemia of Asphyxia and the Part Played Therein by the Suprarenals, J. Physiol. **53**:210, 1919.

60. Sawyer, M. M.; Schlossberg, T., and Bright, E. M.: Studies of Homeostasis in Normal and Sympathectomized Animals: II. The Effect of Anoxemia, Am. J. Physiol. **104**:184, 1933.

61. Kläsi, J.: Ueber die therapeutische Anwendung der Dauernarkose mittels Sommifens bei Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **74**:557, 1921.

62. Quastel, J. H., and Wheatley, A. H.: Narcosis and Oxidations of the Brain, Proc. Roy. Soc., London, s.B **112**:60, 1932.

63. Jowett, M., and Quastel, J. H.: The Effect of Narcotics on Tissue Oxidations, Biochem. J. **31**:565, 1937.

64. Quastel, J. H.: Perspectives in Biochemistry, London, Cambridge University Press, 1937, p. 296.

65. He stated: "There is during narcosis a depressed respiratory metabolism in some part of the nervous system compared with which the metabolic disturbance in the brain giving rise to the original mental disorder is of small magnitude. A new equilibrium will be achieved during narcosis, which will become practically identical in the psychotic individual with that in the normal. When the patient is finally allowed to recover from the narcosis, the nervous system will tend to revert at once to the 'normal'."

of the *Dauerschlaf* treatment. Although it is possible that other factors are involved, it is obvious that the reduction in oxygen consumption by administration of narcotics creates conditions similar to those obtained in hypoglycemia. The main difference between the two procedures lies in the degree of activation of the sympathetic system. This is considerable in hypoglycemia, as clinical and experimental data indicate, and is apparently absent in the narcosis treatment. This may account for the lesser efficiency of the latter treatment and may be due to the fact that the narcotics diminish also the excitability of the hypothalamic and medullary centers. Even under these conditions, however, symptoms of sympatheticoadrenal excitation are not absent. This is evident from the observations of Kulkow and his collaborators,[66] who frequently observed hyperglycemia after awakening.

The third method to be discussed is the metrazol treatment. Meduna [67] introduced this treatment on the basis of the empiric statements (1) that epilepsy associated with schizophrenia is uncommon and (2) that in such cases the prognosis for recovery from schizophrenia is much better than in comparable cases in which epilepsy is absent.

Treatment with metrazol was designed to imitate epileptic convulsions, and this similarity is substantiated by the resemblance of the humoral changes following injections of metrazol and those during epileptic convulsions. An attempt to understand the effects of metrazol on a pathophysiologic basis is omitted, although studies (Bömer [68]) have given a definite indication with regard to the mechanism involved. Bömer observed a rise in blood sugar in rabbits after injections of metrazol, which persisted for some time. Splanchnicotomy, however, prevented it completely. The effect is similar to that of other convulsant drugs and therefore may be secondary to the occurrence of convulsions. That metrazol leads to excitation of the sympatheticoadrenal system is perhaps supported by the fact that it produces dilatation of the pupils, although one must keep in mind that this reaction is not infrequently brought about by parasympathetic inhibition (Ury and Gellhorn [69]).

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66. Kulkow, A. E.; Weiland, W. J., and Kakusina, B. S.: Ueber die humoralen Veränderungen bei der Behandlung der Schizophrenie mit der Dauernarkose, Gemisch nach Cloetta (Cloettal), Schweiz. f. Neurol. u. Psychiat. (supp.) **39**:194, 1937.

67. von Meduna, L.: Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie: I. Campher- und Cardiazolkrämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:235, 1935; Allgemeine Betrachtungen über Cardiazoltherapie, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:32, 1937.

68. Bömer, M.: Ueber die Wirkung einiger Krampfgifte auf Blutzucker und Blutmilchsäure, Arch. f. exper. Path. u. Pharmakol. **149**:247, 1930.

69. Ury, B., and Gellhorn, E.: The Effect of Anoxia on Reflex Dilatation of the Pupil, Proc. Am. Physiol. Soc., 1938, p. 207; Proc. Soc. Exper. Biol. & Med. **38**:426, 1938.

Preliminary experiments on cats with unilateral section of the cervical portion of the sympathetic chain (Gellhorn and Darrow [70]), however, have shown that metrazol leads to an increased sympathetic discharge. This is indicated by contraction of the nictitating membrane and greater pupillary dilatation of the normal eye than that found in the sympathectomized eye. It is important to note that this effect is present even after complete elimination of the convulsions by curare. That the effect described is nervous rather than humoral (epinephrine) is shown by the fact that the denervated nictitating membrane, which reacts readily to epinephrine, does not contract. The effect on the sympathetic system persists for some time and is seen in increased responsiveness of the sympathetic system to afferent nerve stimuli (figs. 4 and 5). These

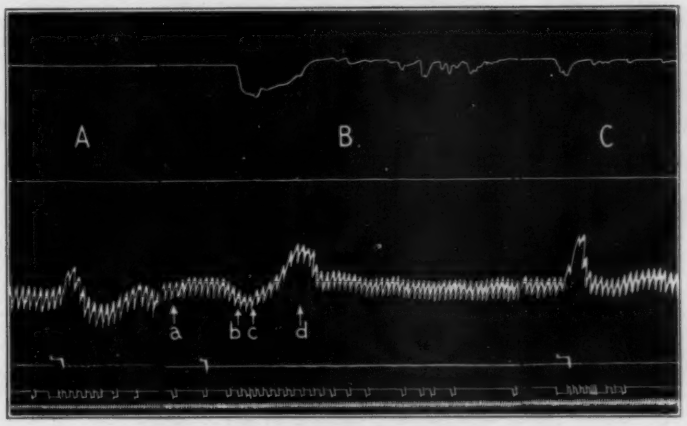

Fig. 4.—Influence of metrazol on cats. Tracings from the top downward are those for the right nictitating membrane; the left nictitating membrane on the sympathectomized side; the blood pressure, and the signal magnet, signifying stimulation of the left brachial plexus (*A* and *C*) with a Harvard inductorium at a distance of 5 cm. for five seconds. The records in *B* were obtained after intravenous injection of 0.4 cc. of a 10 per cent solution of metrazol.

observations agree well with the effects observed in hypoglycemia. The analogy goes even farther. Himwich and his collaborators [71] have shown recently that on account of the great diminution in breathing during metrazol convulsions the oxygen tension of the arterial blood falls rapidly, so that relative anoxia prevails in the body. This effect must, of course, increase the sympathetic discharge considerably.

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70. Gellhorn, E., and Darrow, C.: Unpublished observations.

71. Himwich, H. E.; Bowman, K. M.; Fazekas, J. F., and Orenstein, L. L.: Effect of Metrazol Convulsions on Brain Metabolism, Proc. Soc. Exper. Biol. & Med. **37**:359, 1937.

The fourth method which, at least temporarily, influences schizophrenia favorably is injection of sodium cyanide and the inhalation of a mixture of from 30 to 40 per cent carbon dioxide in oxygen (Loevenhart, Lorenz and Waters [72]). Under each condition the utilization of oxygen is interfered with (Loevenhart). Moreover, sodium cyanide brings about effective excitation of the sympatheticoadrenal system (Møller and Stefansson [73]). For the sake of completeness, I may add that occasionally cocaine has been found to be effective, although only temporarily.[74] It is significant that cocaine is an effective stimulant of the sympathetic division of the autonomic nervous system.

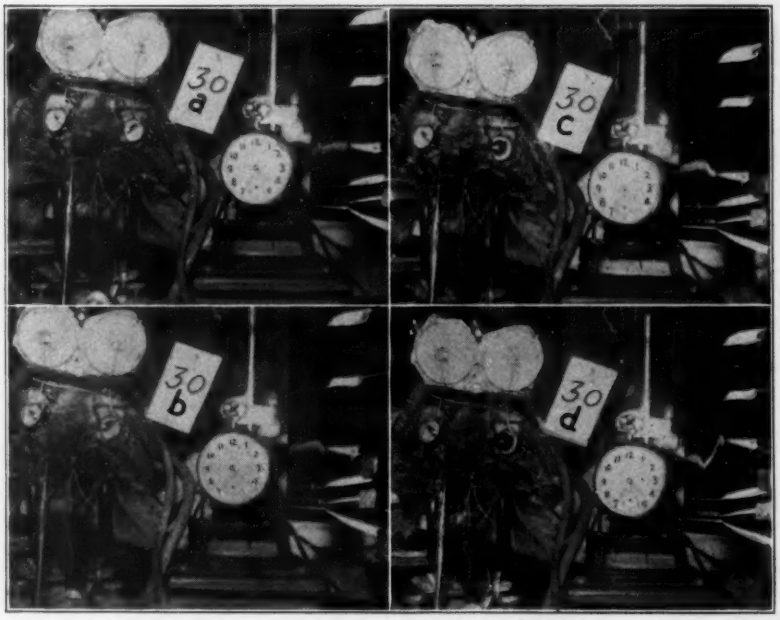

Fig. 5.—Photographs of the left (sympathectomized) and the right (normal) pupil taken at points *a, b, c* and *d,* indicated in figure 4 *B*.

From the brief review of the effects of drugs used with some success in the treatment of schizophrenia, it is evident that, in spite of the fact that these procedures have been introduced for a variety of reasons which do not seem to have anything in common, physiologic analysis shows a remarkable resemblance in the pathophysiologic mech-

72. Loevenhart, A. F.; Lorenz, W. F., and Waters, R. M.: Cerebral Stimulation, J. A. M. A. **92**:880 (March 16) 1929.

73. Møller, K. O., and Stefansson, K.: Ruft Blausäure eine Adrenalinausschüttung hervor? Skandinav. Arch. f. Physiol. **76**:115, 1937.

74. Mayer-Gross, W., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1932, vol. 9, p. 602.

anism which they induce. Hypoglycemia, metrazol convulsions, injections of sodium cyanide, inhalation of high concentrations of carbon dioxide and the *Dauerschlaf* treatment involve an anoxidative state in the brain. Sympathetic discharges are clearly present in hypoglycemia and after administration of metrazol, sodium cyanide, cocaine and carbon dioxide and to some extent in prolonged narcosis. This makes the conclusion probable that the various treatments of schizophrenia are effective because they produce, by profound alteration in the metabolism of the brain, a sufficiently strong and lasting excitation of the sympathetic nervous system.

SCHIZOPHRENIA AND THE SYMPATHETIC NERVOUS SYSTEM

From the preceding considerations an important conclusion must be drawn. If successful treatment of schizophrenia invariably involves excitation of the sympathetic system and if a considerable number of such excitations is necessary to bring about a favorable reaction, a major characteristic of schizophrenia is probably deficient reactivity of the sympathetic nervous system. A number of experimental tests carried out on patients with schizophrenia seem to substantiate this assumption. On the basis of a considerable number of tests referring to changes in pulse rate and blood pressure with change in posture, alterations in body temperature, capillary reactions induced by application of mustard paper to the skin, elimination of water (Volhard's method), sugar tolerance curves and, particularly, changes in the blood sugar after injections of insulin and epinephrine, Pfister [52] concluded that the sympathetic system is hyperexcitable, but weak, in acute stages and deficient in chronic states. Darrow and Solomon [75] found that with increasing improvement schizophrenic patients show greater sweating reactions to standard stimulation. The fact observed by Hoskins [76] that schizophrenic patients exhibit a slight degree of anoxia and, in spite of it, a decrease in respiratory volume and in metabolism may also indicate a deficient response of the sympathetic nervous system, since oxygen deficiency in the normal person sufficiently stimulates respiration and circulation to offset completely the deficient oxygenation of the blood.

Direct clinical observations seem also to support the view that the primary disturbance in schizophrenia is a dysfunction of the autonomic system (Singer [77]). In view of the clinical experience that tumors in the region of the third ventricle produce severe changes in personality

75. Darrow, C. W., and Solomon, A. P.: Personal communication to the author.

76. Hoskins, R. G.: Oxygen Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **38**:1261 (Dec.) 1937.

77. Singer, H. D.: Psychosis and the Central Autonomic Nervous System, J. A. M. A. **110**:2048 (June 18) 1938.

(Alpers [78]) and the well known investigations of Cannon,[79] Bard,[80] and Ranson [81] and many others which show the influence of hypothalamic lesions on emotion and illustrate the mutual interdependence of the hypothalamus and the cerebral cortex, it is understandable, at least in principle, that primary hypofunction and dysfunction of the vegetative centers may profoundly alter cortical functions.

I come, therefore, to the conclusion, based on experimental studies and clinical observations, that schizophrenia involves hypofunction of the sympathetic system and that improvement or cure may be brought about by sufficient stimulation of the sympathetic centers. Since my experiments show that the combination of hypoglycemia and inhalation of gas mixtures poor in oxygen produces particularly effective stimulation of the sympathetic system, its application in the treatment of schizophrenia is recommended. It is of considerable theoretical and practical interest that this combination produces more severe anoxia in the brain than in other organs, such as the heart, lungs and kidneys. This is due to the fact that the brain oxidizes carbohydrates almost exclusively, whereas the other organs can oxidize noncarbohydrate material when the sugar concentration in the blood becomes too low. It will be the task of direct clinical experimentation to determine the most favorable conditions under which insulin hypoglycemia and inhalation of mixtures low in oxygen can be combined. It may be emphasized, however, that this procedure is only one of many possible means of bringing about a strong and lasting discharge over the sympathetic nervous system. Obviously, the sympatheticomimetic drugs, e. g., epinephrine, which act peripherally, are unsuited for this purpose because they tend to diminish the central activity of the sympathetic system. The rise in blood pressure due to administration of epinephrine results in diminished sympathetic activity induced by pressure reflexes originating in the carotid sinus and elsewhere in the body (Heymans, Bouckaert and Wierzuchowski [82]). Moreover, even when epinephrine does not increase the blood pressure, it lowers the activity of the sympathetic centers by means of chemoreflexes from the area of the carotid sinus (Chu and

78. Alpers, B. J.: Relation of the Hypothalamus to Disorders of Personality: Report of a Case, Arch. Neurol. & Psychiat. **38**:291 (Aug.) 1937.

79. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton and Company, 1929.

80. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928.

81. Ranson, S. W.: The Hypothalamus: Its Signfiicance for Visceral Innervation and Emotional Expression, Tr. Coll. Physicians, Philadelphia **2**:222, 1934.

82. Heymans, C.; Bouckaert, J. J., and Wierzuchowski, M.: Reflexes vasomoteurs medullaires d'origine vasculaire barosensible, Arch. internat. de pharmacodyn. et de thérap. **55**:233, 1937.

Hsu [83]). However, drugs or combinations of drugs acting on the sympathetic centers may alone, or in combination with hypoglycemia or anoxia, be of great therapeutic value. There are still other possibilities. As insulin, which is secreted under the influence of the parasympathetic nervous system, elicits a marked sympathetic discharge which probably plays an important part in the effects of hypoglycemia on the central nervous system, so other parasympatheticomimetic drugs may be of therapeutic value. It is assumed, however, that no matter what procedure is chosen the therapeutic effect will not occur unless severe and lasting excitation of the sympathetic centers is brought about, either directly or indirectly. Whether the alteration in the oxidative metabolism of the brain is of specific value or is simply a suitable means of producing sympathetic discharges remains to be seen. In spite of the many problems which are still unsolved, it may be said that if the idea elaborated in this paper is correct, the therapy of schizophrenia will be guided not by empiric findings but by systematic investigations proceeding in accordance with a definite plan, which is based on a physiologic theory of the disease process and on precise physiologic and pharmacologic studies of the drugs used.

SUMMARY AND CONCLUSIONS

Experimental investigations carried out on man, the dog and the rat are reported to substantiate the theory that the oxidative metabolism of the brain is diminished in hypoglycemia. The following facts are shown:

1. A relatively mild degree of anoxia (produced in a low pressure chamber) precipitates insulin convulsions, although these convulsions may be absent or occur much later when the animal is given an injection of the same amount of insulin at normal atmospheric pressure.

2. This increased sensitivity to oxygen deficiency occurs in spite of the fact that the combination of oxygen deficiency and insulin does not lower the level of the blood sugar more than is observed when the same amount of insulin is given under ordinary atmospheric conditions.

3. The rise in blood pressure on inhalation of a gas mixture low in oxygen is greatly increased in the presence of hypoglycemia. This reaction is in proportion to the degree of hypoglycemia but not to the amount of insulin administered.

4. The reaction described in paragraph 3 is reversible on restoration of the level of the blood sugar by administration of glucose. Levulose is partially effective, but galactose is not effective at all.

83. Chu, L. W., and Hsu, F. Y.: The Effect of Adrenaline on Vasomotor Reflexes, Quart. J. Exper. Physiol. **27**:307, 1938.

5. The increased response of the blood pressure observed in narcotized dogs with hypoglycemia on inhalation of low concentrations of oxygen is due to increased sympathetic discharges. Ligation of the adrenal veins does not materially influence this reaction.

6. The response in blood pressure to increased intracranial pressure is increased during inhalation of low concentrations of oxygen. A similar reaction is observed during hypoglycemia and the inhalation of atmospheric air. Each reaction is completely reversible on inhalation of air and injection of dextrose respectively.

7. Another series of investigations is in accord with the theory that insulin hypoglycemia diminishes the oxidative metabolism of the brain. The respiratory volume increases in hypoglycemia as it does in anoxia. It is shown (in man and dogs) that during hypoglycemia the carbon dioxide tension of alveolar air and of arterial blood falls and is restored by injection of dextrose.

8. In the light of these experiments, the major therapeutic procedures used with success in the treatment of schizophrenia are discussed. In contradistinction to the various empiric interpretations by various authors, it is emphasized that all successful treatments of schizophrenia produce stimulation of the sympatheticoadrenal system. In a majority, a state of lowered oxidative metabolism of the central nervous system is either wholly or partially responsible for this stimulation. It is shown that metrazol produces sympathetic excitation even in conditions under which the convulsions are eliminated (curarization).

9. If, as has been shown, successful treatment of schizophrenia is in essence due to nothing other than strong and lasting excitation of the sympathetic division of the autonomic system, involving profound alteration in the oxidative metabolism of the brain, it is to be expected that deficiency in the reactivity of the sympathetic system is a basic feature of schizophrenia. This is indeed shown both by clinical experimentation and by observation. It is assumed that alterations in cortical functions are secondary. This conclusion, too, is supported by clinical and experimental evidence.

10. The experimental studies reported in this paper and the critical considerations furnish a rational physiologic basis for the future therapy of schizophrenia. Since it has been found that the combination of hypoglycemia and oxygen deficiency produces greater stimulation of the sympathetic system than even complete asphyxia, without endangering cardiovascular and respiratory functions, this method is recommended for the treatment of schizophrenia. Details as to the most suitable procedure will be reported later. Moreover, a systematic investigation of various drugs exciting the sympathetic centers is suggested as the basis for a rational therapy of schizophrenia. Such drugs may be of great therapeutic value when administered either alone or in combination with one of the standard procedures.

Case Reports

CLINICAL RESULTS WITH ELSBERG'S OLFACTORY TEST

ALEXANDRA ADLER, M.D., AND KNOX H. FINLEY, M.D., BOSTON

Elsberg [1] has recently described a new method for the physiologic and clinical study of olfaction. The instruments and the procedure used have been described by him,[2] and we have followed his technic in detail. His most important methods for clinical purposes consist in determination of (1) the minimal identifiable odor, or the smallest amount of air mixed with odor, expressed in cubic centimeters, necessary for recognition on one side of the nose and (2) the "olfactory fatigue," which is the refractory period elapsing after a certain degree of fatigue has been produced until the odor can again be perceived. Elsberg found an increase in the value for the minimal identifiable odor in cases of cerebral tumor which produces direct or indirect pressure on the olfactory tract and an increase in olfactory fatigue on the same side as the lesion in cases of tumor within the cerebral hemisphere.

With these findings, Elsberg pointed out that the sense of smell can be used for the localization of tumors of the brain to better advantage than has previously been recognized.

The following findings are the results of our application of Elsberg's olfactory test in cases of tumor of the brain.[3]

RESULTS OF STUDY

Our studies with normal subjects used as controls showed that the value for the minimal identifiable odor for coffee and citral was in no case higher than that cited by Elsberg [4] (9 cc. for coffee and 8 cc. for citral). However, we fre-

From the Department of Neurology, Harvard University Medical School; the Neurological Unit, Boston City Hospital, and the Neurological Service, Massachusetts General Hospital.

1. Elsberg, C. A.: The Newer Aspects of Olfactory Physiology and Their Diagnostic Applications, Arch. Neurol. & Psychiat. **37**:223 (Feb.) 1937.

2. Elsberg, C. A., and Brewer, E. D.: The Sense of Smell: X. A Detailed Description of the Technique of Two Olfactory Tests Used for the Localization of Supratentorial Tumors of the Brain, Bull. Neurol. Inst. New York **4**:501 (Dec.) 1935.

3. We carried out these studies independently in different institutions (A. A., in the Boston City Hospital and the New England Deaconess Hospital, and K. H. F., in the Massachusetts General Hospital). As the results are in general agreement, they are combined in this report.

4. Elsberg, C. A.: The Sense of Smell: XI. The Value of Quantitative Olfactory Tests for the Localization of Supratentorial Tumors of the Brain; a Preliminary Report, Bull. Neurol. Inst. New York **4**:511 (Dec.) 1935; XII. The Localization of Tumors of the Frontal Lobe of the Brain by Quantitative Olfactory Tests, ibid. **4**:535 (April) 1936.

quently found that the value for the minimal identifiable odor for normal subjects was less than these amounts, that is from 3 to 4 cc. for coffee and citral. Needless to say, attention was given to see that the patient held his breath while the minimal identifiable odor was determined. The same results were obtained with olfactory fatigue. Its values did not exceed those obtained by Elsberg,[5] i. e., from two to two and one-half minutes for coffee and from two to three minutes for citral, but often were lower, i. e., one and one-half minutes and sometimes even one-half minute.

The results of the examination of smell with this new method in cases of tumor of the brain verified by operation or autopsy are given in the accompanying tables.

TABLE 1.—*Data in Cases of Extracerebral Tumors in the Subfrontal Region Associated with Signs*

Case No.	Coffee				Citral				Location	Diagnosis
	Minimal Identifiable Odor		Olfactory Fatigue		Minimal Identifiable Odor		Olfactory Fatigue			
	Right	Left	Right	Left	Right	Left	Right	Left		
1	..	..	..	..	5	5	1	1.5	Right	Supraorbital meningioma
2	14	12	1.5	1	5	5	1.5	1	Right	Pituitary adenoma piercing capsule
3	..	..	..	..	4	5	1	1	.....	Suprasellar cyst
4	5	25	2	2.5	4	0	1.5	...	Left	Glioma of optic nerve and chiasma
5	10	9	0.5	1	5	5	0.5	1	.....	Pituitary adenoma with atrophy of optic nerve
6	30	11	..	2.5	12	7	1	1	Right	Hemangioma of the frontoparietal region, extending to base
7	3	3	..	..	..	..	...	...	Right	Tumor of the sphenoid ridge
8	4	9	..	..	2	6	1.5	1	.....	Pituitary tumor with changes in visual fields and sella
9	5	5	..	..	3	3	1	1	.....	Pituitary tumor with changes in visual fields and sella

As compared with Elsberg's results, who found the value for the minimal identifiable odor to be elevated in 24 of 25 cases of subfrontal tumor, we found an elevated value in 3 of 7 cases of growth in the same location. The increase was observed, in accordance with Elsberg's findings, on the side of the tumor.

In addition to the cases in table 1, there were normal values for the minimal identifiable odor and olfactory fatigue in 3 cases of verified pituitary tumor in which there were no associated signs and the tumor did not extend beyond the limits of the sella.

The cases in which there was complete unilateral loss of smell, whether caused by extracerebral or intracerebral growths, are not mentioned in the tables.

Elsberg stated that increased olfactory fatigue is found in cases of intracerebral tumor or a large dural growth buried in the brain. He cited 27 such

5. Elsberg, C. A.: The Sense of Smell: VIII. Olfactory Fatigue, Bull. Neurol. Inst. New York **4**:479 (Dec.) 1935.

TABLE 2.—*Data in Cases of Dural Tumors Buried in the Cerebral Substance or Intracerebral Tumors*

Case No.	Coffee: Minimal Identifiable Odor Right	Coffee: Minimal Identifiable Odor Left	Coffee: Olfactory Fatigue Right	Coffee: Olfactory Fatigue Left	Citral: Minimal Identifiable Odor Right	Citral: Minimal Identifiable Odor Left	Citral: Olfactory Fatigue Right	Citral: Olfactory Fatigue Left	Location	Diagnosis
1	2	2	..	..	3	4	2.5	2.5	Left	Abscess of frontal lobe
2	9	9	2	1	5	4	1	1	Right	Meningioma of frontal lobe
3	12	13	2	2	7	7	2	1.5	Left	Abscess of frontal lobe
4	10	7	1	2.5	7	7	2	1	Left	Parasagittal meningioma of frontal lobe
5	11	8	2	1.5	8	8	1	2	Left	Glioblastoma of frontoparietal region
6	6	8	1.5	2	..	..	...	...	Left	Glioma of parietofrontal region
7	4	4	..	..	4	5	2.5	2.5	Right	Glioma of frontal lobe
8	3	3	..	..	3	4	3.5	6.5	Left	Abscess of frontal lobe
9	9	8	1	1	8	7	1	1	Left	Astrocytoma of frontoparietooccipital region
10	30	11	..	2.5	12	7	1	1	Right	Hemangioma of frontoparietal region, extending to base (table 1, case 6)
11	3	6	..	..	4	6	1	0.5	Left	Tumor of frontoparietal region
12	9	17	2	1	16	18	1	1	Left	Parasagittal meningioma of occipitoparietal region
13	10	7	2	2	5	7	2.5	2	Bilat.	Spongioblastoma of parietooccipital region
14	5	5	0.5	0.5	4	5.5	0.5	0.5	Left	Glioma of temporal lobe
15*	30+	6	..	..	30+	8	...	2.5	Left	Glioma of parietal lobe

* Obstruction of the right nasal passage due to a deviated septum was present in this case.

TABLE 3.—*Data in Cases of Tumors of the Posterior Fossa*

Case No.	Coffee: Minimal Identifiable Odor Right	Coffee: Minimal Identifiable Odor Left	Coffee: Olfactory Fatigue Right	Coffee: Olfactory Fatigue Left	Citral: Minimal Identifiable Odor Right	Citral: Minimal Identifiable Odor Left	Citral: Olfactory Fatigue Right	Citral: Olfactory Fatigue Left	Location	Diagnosis
1	3	3	2	1	3	4	2	2.5	.....	Tumor of posterior fossa
2	2	5	0.5	1.5	1	5	0.5	1	Right	Cerebellar astrocytoma
3	5	5	0.5	1	6	6	0.5	0.5	Left	Hemangioma of medulla
4	3	3	..	..	3	3	1	1	.....	Medulloblastoma of fourth ventricle
5	7	5	1	1	5	6	0.5	0.5	.....	Midline cerebellar tumor
6	2	3	..	..	2	2	1.5	1.5	.....	Tumor of posterior fossa
7	..	..	..	..	6	5	2	1.5	Right	Acoustic neuroma
8	..	..	..	..	6	6	2.5	2	Left	Acoustic neuroma

cases (tables 4 and 5[4]). Our 16 cases listed in table 2 belong in this group. In 1 of them there was increase in the olfactory fatigue. This was bilateral, but was more marked on the side of the tumor. The combination of unilateral elevation of the value for the minimal identifiable odor and prolonged fatigue described as characteristic for tumors within the substance of one frontal lobe, which "directly or indirectly" exert pressure on the olfactory tracts,[1] has not been found in our cases. The value for the minimal identifiable odor was elevated in 3 of 9 cases of tumor of the frontal lobe, but the olfactory fatigue was normal. In 1 of them (case 10) the tumor exerted direct pressure on the olfactory tract. Elsberg would classify the tumors in the other 2 cases with those causing indirect pressure on the olfactory tract.

Elsberg pointed out that the value for the minimal identifiable odor is decreased frequently in cases of tumor of the posterior fossa because of increased intracranial pressure, which produces greater irritability of the olfactory pathways. Table 3 shows the values for the minimal identifiable odor and olfactory fatigue in 9 cases of tumor of the posterior fossa. Though suggestive in some instances, our findings do not give conclusive evidence that one can expect a decrease in value for the minimal identifiable odor in such cases with any reliability, particularly since in our determinations made as controls, as was mentioned before, low values also were frequently shown.

In agreement with Elsberg, one of us (A. A.) also found an increased value for the minimal identifiable odor not only in cases of tumor but in some cases of different types of cerebral lesions, such as basal meningitis, hemorrhage and generalized arteriosclerosis of the brain.

An endeavor was made to perform the olfactory test on every patient with a cerebral tumor admitted to the hospital. However, one of us (K. H. F.) found that only 55 per cent of all patients with tumors of the brain were mentally clear enough to cooperate accurately for the test.

SUMMARY

The Elsberg olfactory test enables one to determine quantitatively the olfactory function. In 3 of our 7 cases of tumor exerting direct pressure on the olfactory tract the value for the minimal identifiable odor was, in accordance with Elsberg's findings, increased on the same side as the growth, suggesting that this part of the test is of diagnostic help in some cases. The occurrence of increased olfactory fatigue in cases of intracerebral tumors seems to be too rare (in 1 of 16 cases) to be of practical value for localization of tumors of the brain.

Dr. Gilbert Horrax permitted us to examine his patients at the Lahey Clinic by this method.

HYPERTROPHIC INTERSTITIAL NEURITIS WITH PAPILLEDEMA

A. W. Diddle, M.D., and R. L. Stephens, M.D., Iowa City.

Our purpose in the present communication is to place on record the first case of interstitial hypertrophic neuritis diagnosed among 138,213 patients admitted to the University Hospitals during ten years, from 1926 to 1936. The diagnosis was confirmed by histologic examination of a portion of an affected nerve removed for biopsy. In addition, the case is of interest because of the presence of bilateral papilledema, the history of one remission and the high total protein content of the cerebrospinal fluid.

Interstitial hypertrophic neuritis was first described by Dejerine and Sottas.[1] The symptoms and signs observed by them included miosis, the Argyll Robertson pupil, lightning pains in the extremities, motor ataxia, fibrillary twitchings, nystagmus and general muscular atrophy. There was absence of intention tremor, scanning speech and exophthalmos. The onset of the disease was usually in infancy or early adulthood. In contradistinction to the preceding syndrome, Marie[2] and Boveri[3] stressed the familial aspect of the disease. They observed the onset of symptoms in adulthood. Objectively, there was no Romberg sign, miosis or Argyll Robertson pupils, and the pupils reacted slowly to light. There were intention tremor, scanning speech and exophthalmos. Muscular atrophy was limited to the lower extremities, with slight involvement of the intrinsic muscles of the hands. There were no lightning pains in the legs, motor ataxia, nystagmus or fibrillary twitchings of the muscles. Pathologically, the disease often gave the appearance of multiple sclerosis. The sympathetic, cranial and peripheral nerves were affected, with associated leptomeningitis of the cord (Marie and Bertrand[4]; Souques[5]).

Only 55 cases have been recorded prior to the time of writing (Schaller and Newman[6]; Villaret and others[7]; Cooper,[8] and Ornsteen

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From the Department of Neurology, the State University of Iowa.

Drs. C. E. Van Epps and A. L. Sahs furnished suggestions and records.

1. Dejerine, J., and Sottas, I.: Sur la névrite interstitielle hypertrophique et progressive de l'enfance, Compt. rend. Soc. de biol. **5**:63, 1893.

2. Marie, P.: Forme spéciale de névrite interstitielle hypertrophique progressive de l'enfance, Rev. neurol. **14**:557, 1906.

3. Boveri, P.: De la névrite hypertrophique familiale, Semaine méd. **30**:145, 1910.

4. Marie, P., and Bertrand, I.: Contribution a l'anatomie pathologique de la névrite hypertrophique familiale, Ann. de méd. **5**:209, 1918.

5. Souques, A.: Forme atypique de névrite hypertrophique progressive, Ann. de méd. **19**:484, 1926.

(Footnotes continued on next page)

and Sloane [9]). The diagnoses in 25 were confirmed by histologic examination of sections secured either for biopsy or at autopsy. In 11 of the remaining 30 unverified cases, such atypical histories were presented that it cannot be decided with certainty whether the condition was interstitial hypertrophic neuritis.

REPORT OF A CASE

History.—A man aged 26, unmarried, a farmer, entered the University Hospitals on March 5, 1937, complaining of pain, numbness and weakness of the arms and legs. Because of this, walking had become increasingly difficult in the past two years. The patient also had noticed intermittent blurring of vision during the three years prior to admission. During the fall of 1933 he observed numbness and stinging sensations in the hands and fingers and for two months was unable to grasp objects with certainty. After this he was practically without symptoms for three months, only again to have impairment of body function, with shooting, aching pains in the hands. Within a year after onset, the numbness and aching began to involve the feet, and subsequently strength in both the hands and the feet diminished. Soreness and tenderness in the muscles of the lower extremities prevented sitting with the legs crossed, as the weight of one extremity on the other was unbearable. In the fall of 1935 the patient expressed the belief that the arches of both feet were higher; he walked with a shuffling gait and experienced difficulty in maintaining balance. Although the pain and soreness gradually disappeared within the next few months, the muscular weakness steadily increased.

At about the same time he was examined in another clinic,[10] where he was found to have profound polyneuritis, which apparently, however, included only one of the cranial nerves—the optic. Examination of the visual fields revealed that the blindspot in the right eye was enlarged and that in the left eye was normal. There was papilledema, of 2 diopters, on the left side. The temporal side of the right fundus was paler than normal and showed loss of substance, while on the nasal side there was residual edema. Marked muscular weakness, most marked distally, was present in all the extremities, and fibrillary twitchings were scattered throughout the muscles. The deep reflexes in the arms were diminished, but could be obtained. Areflexia was present in the lower limbs, and there was akinesthesia extending up the legs to the hips. It was also noted that the peripheral nerves were tender. Examination of the spinal fluid gave negative Kolmer and Kline reactions, a total protein content of 800 mg. per hundred cubic centimeters, a positive reaction for globulin and 7 lymphocytes per cubic millimeter. Tests for the presence of lead and arsenic in the urine gave negative results.

After this examination and for the four months preceding his admission to the University Hospitals he had been unable to wiggle the toes or button his clothes because of weakness of the muscles, and for the first time, in January

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6. Schaller, W. F., and Newman, H. W.: Névrite interstitielle hypertrophique, Rev. neurol. **63**:529, 1935.

7. Villaret, M.; Haguenau, J., and Klotz, P. H.: Névrite hypertrophique familiale, Rev. neurol. **63**:211, 1935.

8. Cooper, E. L.: Progressive Familial Hypertrophic Neuritis (Dejerine-Sottas), Brit. M. J. **1**:793, 1936.

9. Ornsteen, A. M., and Sloane, P.: Hypertrophic Interstitial Neuritis of Dejerine and Sottas, Arch. Neurol. & Psychiat. **37**:466 (Feb.) 1937.

10. Dr. F. P. Moersch supplied us with the findings at that time.

1937, he noted that he could not whistle. He expressed the belief that he had not had fever, diplopia, diarrhea, spinal curvature, exophthalmos, dysphagia or disturbances in the rectal and vesical sphincters. There was no known exposure to arsenic or lead. The weight had declined from 135 to 115 pounds (61.2 to 57.2 Kg.) during the period of four years.

The patient used alcohol and tobacco in moderation preceding the onset of the disease. He claimed never to have had a venereal infection. The father, mother and 7 siblings were reported to be in good health; 1 brother aged 15 years has pes cavus, but is without symptoms. The patient's past history included an attack of smallpox at the age of 21, with uneventful recovery. The tonsils were removed at the age of 25. There was no history of serious injury. Since the age of 12 he has had occasional attacks of dull frontal headache.

Physical Examination.—On admission to the hospital the patient measured 156 cm. in height and weighed 51.8 Kg. He was fairly well nourished, but was weak and chronically ill; he was oriented as to time, place and person. There were no difficulties in speech. The contour of the head was normal; he could not wrinkle his forehead. The pupils measured 4 mm. on the right and 5 mm. on the left; their outlines were regular. The reaction to light was slight, and that in accommodation was about one-half normal on each side. Horizontal nystagmoid movements were present. Both fundi showed choked disks, 2 diopters on the right and 3 diopters on the left. Slight temporal atrophy was present in the right disk. The visual field on the right was moderately constricted. Without correction, vision on the right was 6/12—1 and on the left 6/6. The strength of the orbicularis oculi muscles was estimated to be diminished one-half. Air conduction in the ears was normal. The Weber and Rinne tests for conduction of sound gave normal results. The patient was unable to pucker the mouth sufficiently to whistle. Showing the teeth was performed with difficulty, while biting movements were unimpaired. Movements of the palate and tongue were symmetric and equal, and taste and smell sensations were elicited as usual. The chest was symmetric and of asthenic type and expanded well on inspiration. The apical heart beat was felt 10 cm. to the left of the midsternal line, in the fifth interspace and within the midclavicular line. There was no arrhythmia, murmur, thrill or deficit in pulse, and the heart rate was 91 beats per minute. The systolic blood pressure was 110 mm. of mercury, and the diastolic, 90 mm. The lungs were clear to percussion and auscultation. Examination of the abdomen and genitalia revealed no abnormalities. Tone of the rectal sphincter was normal. Kyphoscoliosis was not evident externally. Weakness of the muscles of the neck and arms could not be demonstrated, while movements in the hands and fingers were clumsy; the hand grips were reduced markedly. The Aran-Duchenne type of atrophy was present in the hands, while there was moderate winging of the scapulas. The tone of the forearms was reduced about one-half. Gross tests revealed no weakness of the muscles of the trunk. Examination of the legs disclosed moderate atrophy of the muscles, with sharpening of the shins and pes cavus bilaterally. Muscular strength in the toes and ankles was negligible; there was no tenderness. Active extension and flexion of the knees and hips were performed with an estimated efficiency of 50 and 100 per cent, respectively. The gait was ataxic and of steppage character, and the Romberg sign was elicited. Rapid voluntary alternating movements were performed badly. There was ataxia in the finger to nose and heel to knee tests. Investigation of the sensory nerves revealed hypesthesia, of a glove and stocking type, more marked distally. The supraorbital, jaw, knee, ankle, plantar, abdominal and cremasteric reflexes could not be elicited. The biceps and triceps reflexes were present, but greatly diminished. The most important finding was the enlarged, firm nerve trunks of

the cervical and brachial plexuses. Those in the neck could be seen and readily palpated by having the patient rotate his head to one side or the other (fig. 1).

Laboratory Findings.—Examination of the urine recorded nothing abnormal except the presence of 22 mg. of lead in a twenty-four hour specimen. The quantity compatible with absence of symptoms is 50 mg. Studies of the blood smears disclosed a normal picture, with a differential count of 70 per cent neutrophils, 24 per cent lymphocytes and 6 per cent mononuclears. The red cell count was 5,090,000, and the white cell count 10,850 cells per cubic millimeter. The hemoglobin, as determined by the Haden-Hausser method, was 15 Gm. The Wassermann and Kahn reactions both of the blood and of the spinal fluid were negative. The spinal fluid on two occasions was clear, but contained from 438 to 530 mg. of protein per hundred cubic centimeters. There were no cells, and Meyer's test revealed no blood. Initial pressures were 200 and 240 mm. of water,

Fig. 1.—Photograph of the patient, showing the hypertrophied nerves in the neck.

respectively. With the Queckenstedt test the pressure rose to 370 mm. of water. Fluoroscopic and stereoscopic examinations of the chest revealed nothing abnormal. Films of the skull revealed no abnormal areas of rarefaction or calcification except in the occipital regions, where there was thinning of the skull. The sella turcica was well visualized and within normal limits. The pineal body was not calcified. Anteroposterior and lateral views of the cervical, thoracic and lumbar vertebrae showed no scoliosis. Electrical reactions with faradic stimulation were definitely reduced in all the extremities. The reaction of degeneration (ACC > CCC) was demonstratable in the right leg and thigh. Over the other extremities the galvanic reactions were diminished.

Course in the Hospital.—Physical examination at frequent intervals disclosed few changes in the clinical findings over two months. From time to time the patient complained of sensations of fibrillary tremors; however, none was observed. Often, dull aching pains in the legs and arms prevented him from sleeping. Relief was obtained in most instances by the application of heat, either in the form of hydrotherapy baths or locally with the inductotherm. Muscular strength remained about the same, and long leg braces were fitted to improve walking. On March

25 he observed difficulty in swallowing. Examination by otolaryngologists showed chronic simple laryngitis with second degree paralysis of the left vocal cord. From March 30 to April 3 a total of 1,500 roentgen units was given to the right brachial plexus in five equally divided doses. At the time of the fourth exposure the patient experienced less pain in the right arm. However, pain in the right arm increased in severity on April 16. Objectively, we were not able to confirm any change in the sensory and motor phenomena of the arm or in the size of the nerves. Since all types of therapy gave temporary relief from pain, it was thought that the subjective improvement was psychologic, not physiologic.

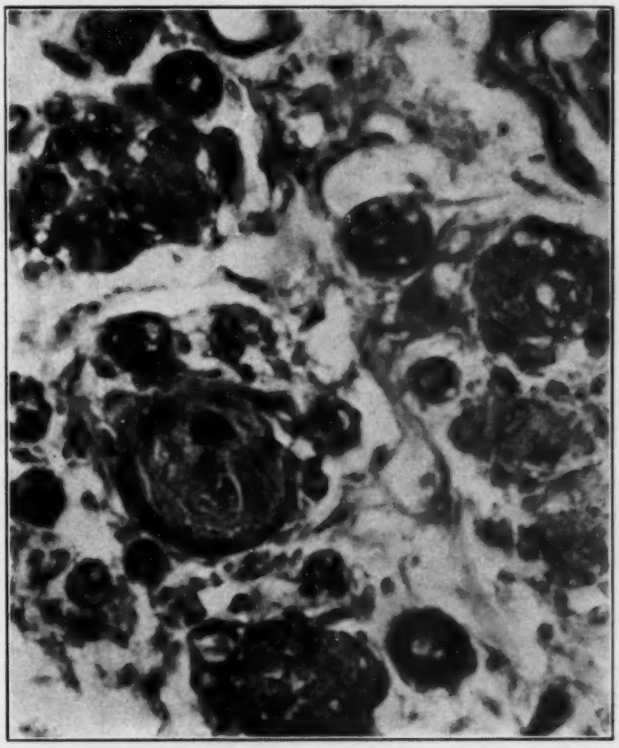

Fig. 2.—Photomicrograph of a section from the greater auricular nerve, showing the typical "onion bulb" formations and the relatively few axons. Weigert's silver stain; × 900. Permission of Dr. Gregory Barer.

Before discharge on April 28, vision was reported as approximately normal bilaterally. The papilledema on the right had receded 1 diopter, and the temporal quadrant of the fundus was white and atrophic. There was no change in the fundus of the left eye. The light reaction was slightly better than at the time of admission.

Pathologic Condition.—On March 9, with the use of local anesthesia, a portion of the right greater auricular nerve was taken for biopsy. Grossly, it was smooth, firm and glistening and was enlarged to five or six times the normal size. Microscopic sections stained by the Delafield hematoxylin, Masson and Weigert methods revealed moderate thickening of the epineurium, which was made up of concentrically arranged layers of fibroblasts and collagen (fig. 2). The nuclei of the

perineurium were condensed, hyperchromatic and elongated. The perineurium, which was myxomatous, contained many compact bundles of fine, netlike, delicate fibers running in various directions. An occasional fibroblast was seen within the meshes of the strands. In many instances the nerves were replaced by bundles of collagenous concentric laminated structures resembling an onion bulb. These were compact toward the center and loose at the periphery. Many of the axons within the myelin sheaths were missing, while some of the sheaths appeared granular. In other instances there was an increase in the number of nuclei in the periaxonal tissue.

COMMENT

This disease has already been adequately described clinically,[11] historically [6] and pathologically.[12] It has received more general attention by Wolf, Rubinowitz and Burchell.[13] Therefore, the details will not be repeated.

Clinically, our patient showed the typical course and symptoms of the disease described by Dejerine and Sottas, except for the papilledema and the history of one remission during the first year of the malady.

Two other cases, in 1 of which the diagnosis was proved histologically, have been reported as those of recurring polyneuritis.[14] Harris and Newcomb [14b] recorded a case in which there were recurrent attacks of polyneuritis for six years with complete recovery between episodes. The last attack, of twelve months' duration, was progressive, with muscular wasting, followed by paralysis of the diaphragm. The deep reflexes were absent, and sensation was not affected. At autopsy the typical onion bodies were observed in the nerves.

In 2 instances involvement of the optic nerves has been described. Souques [5] observed pallor of the temporal side of the fundi in a woman aged 58. Histologically, the optic nerves were infiltrated with interstitial tissue. Wolf, Rubinowitz and Burchell [13] observed a case in which there were concentric contraction of both visual fields and pallor of both optic disks. The other cranial nerves were normal.

Cases in which there was a high total protein content of the cerebrospinal fluid comparable with our findings have thus far not been reported. In our case there was considerable variation in the amount over a period of six months. It is conceivable that the protein level depends on the acuteness of the degenerative phase of the disease. Hewitt [15] and Wilcox [16] found this to be true in cases of acute and

11. Dejerine and Sottas.[1] Marie.[2] Boveri.[3] Ornsteen and Sloane.[9]

12. Bielschowsky, M.: Familiäre hypertrophische Neuritis und Neurofibromatose, J. f. Psychol. u. Neurol. **29**:182, 1922. Marie and Bertrand.[4]

13. Wolf, A.; Rubinowitz, A. H., and Burchell, S. C.: Interstitial Hypertrophic Neuritis of Dejerine and Sottas, Bull. Neurol. Inst. New York **2**:373, 1932.

14. (*a*) Nattrass, F. J.: Recurrent Hypertrophic Neuritis, J. Neurol. & Psychopath. **2**:159, 1921-1922. (*b*) Harris, E., and Newcomb, W. D.: A Case of Relapsing Interstitial Hypertrophic Polyneuritis, Brain **52**:108, 1929.

15. Hewitt, L. F.: Proteins of the Cerebrospinal Fluid, Brit. J. Exper. Path. **8**:84, 1912.

16. Wilcox, H. B.; Lyttle, J. D., and Hearn, J. E.: The Chemical Composition of the Spinal Fluid; Diagnostic Value, Am. J. Dis. Child. **30**:513 (Oct.) 1925.

chronic inflammatory lesions of the meninges due to various etiologic factors.

The question arises: Is the pathologic lesion encountered in hypertrophic interstitial neuritis neoplastic or inflammatory? In the light of the newer concepts of the pathologic change, namely, that proliferation is that of the Schwann sheath cells, and of the resemblance of the "onion bulb" formations observed in cases of neurofibromatosis to those in the present case, Schaller and Newman [17] expressed the belief that the lesion was neoplastic. From this point of view, they treated their patient by exposing some of the peripheral plexuses on one side of the body to small doses of roentgen rays; the opposite side was used as a control. The results of their therapy were equivocal. Subsequent observations were not available to decide whether the amount of radiation was insufficient to produce a recognizable clinical change or totally ineffective as a therapeutic measure.

Wolf and others [13] concluded that the inflammatory changes in the perineurium are incidental to degeneration of the myelin sheaths and axons. In view of the report of Schob,[18] who observed "onion bulb" formations in cases of multiple sclerosis, they expressed the belief that the characteristic lesion of hypertrophic interstitial neuritis becomes less illuminating. However, they ended by saying:

> The original name given by Dejérine and Sottas "interstitial hypertrophic neuritis" seems acceptable to us even though the Schwann cell origin of the disease is conceded, since the Schwann apparatus is a supporting interstitial structure.

SUMMARY

A case of hypertrophic interstitial neuritis, with the clinical and pathologic observations at biopsy, is described. The principal clinical findings of significance were: glove and stocking type of hypesthesia; partial paralysis and muscular atrophy of the extremities; hypertrophy of the peripheral nerves, and moderate loss of vision. Associated with this were bilateral papilledema and increase in the cerebrospinal fluid pressure and the total protein content of the spinal fluid. The reflexes were diminished or absent. Fibrillary tremors were observed at an earlier stage in the disease. During the period of observation difficulty in swallowing, with secondary paralysis of the left vocal cord, developed. As a therapeutic measure, 1,500 roentgen units was given over the right brachial plexus, with the left side as a control. Clinically, there was no improvement.[19]

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17. Schaller, W. F.: Personal communication to the authors. Schaller and Newman.[6]

18. Schob, F.: Wurzelfibromatose bei multipler Sklerose, München. med. Wchnschr. **59**:1831, 1912.

19. The patient was again seen on Feb. 22, 1938. Symptomatically he was slightly improved, with no further pain. The physical and laboratory findings were essentially as described on the first admission except for progressive wasting of the musculature of the extremities. There was little strength left in the hands. The nerves in the popliteal spaces were now palpable. There was no evidence of improvement from the roentgen therapy.

Technical and Occasional Notes

NEW MODIFICATIONS OF THE BENZIDINE STAIN FOR STUDY OF THE VASCULAR PATTERN OF THE CENTRAL NERVOUS SYSTEM

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BOSTON

The benzidine stain demonstrates the vascular pattern by selective staining of the red blood cells contained in the vessels. Lepehne [1] first employed the principle of the method, namely, the benzidine test for hemoglobin, for the purpose of specifically staining hemoglobin in tissue sections; he noted that the resultant picture may resemble injection of the vessels. Later, Sjöstrand [2] used a benzidine stain in his studies of blood depots in the lungs and liver, and Lindgren,[3] in his studies on the amount of capillaries in brain tissue of young and old persons, referred to the stain as Sjöstrand's method. Pickworth,[4] however, was the first to adapt the principle to the specific object of demonstrating the cerebral vascular pattern, especially by use of thick frozen sections. The method consists essentially in applying the benzidine test for hemoglobin (peroxidase reaction) to frozen sections of from 200 to 300 microns in thickness. In addition to the red cells, the polymorphonuclear leukocytes, but no other tissue elements, are stained. Recently Campbell, Alexander and Putnam [5] and Alexander and Campbell [6] have used a slight modification of Pickworth's method, which they evolved mainly by abbreviating the procedure.

The expenses of this investigation were defrayed in part by the Multiple Sclerosis Fund of Harvard University.

From the Neurological Unit, the Boston City Hospital, and the Department of Neurology, Harvard University Medical School.

1. Lepehne, G.: Zerfall der roten Blutkörperchen beim Icterus infectiosus (Weil): Ein weiterer Beitrag zur Frage des hämatogenen Icterus, des Hämoglobin- und Eisenstoffwechsels, Beitr. z. path. Anat. u. z. allg. Path. **65**:163-226, 1919.

2. Sjöstrand, T.: Funktionieren die Leber und die Lunge als Blutdepots? Klin. Wchnschr. **13**:169-173, 1934.

3. Lindgren, Å. G. H.: Quantitative Untersuchungen über den Kapillarengehalt der grauen Substanz des Gehirns bei jungen und alten Menschen, J. f. Psychol. u. Neurol. **47**:492-509, 1937.

4. Pickworth, F. A.: A New Method of Study of the Brain Capillaries and Its Application to the Regional Localization of Mental Disorder, J. Anat. **69**:62-71, 1934.

5. Campbell, A. C. P.; Alexander, L., and Putnam, T. J.: The Vascular Pattern in Various Lesions of the Human Central Nervous System: Studies with the Benzidine Stain, Arch. Neurol. & Psychiat. **39**:1150-1203 (June) 1938.

6. Alexander, L., and Campbell, A. C. P.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229-248, 1937.

There can be no doubt that Pickworth's modification of the method, in which an aqueous solution of benzidine is used, is superior to Lepehne's original method in that it stains the vascular contents deep black, thus providing clearcut pictures which are easily interpreted and satisfactorily photographed.

The method, however, is difficult and complicated, and sometimes refuses to yield satisfactory results even in the hands of an experienced worker. Lepehne, in his original method, used an alcoholic solution of benzidine. This is not as successful as the aqueous solution used by Pickworth in that it stains the vascular contents brown and produces a less clearly defined picture.

In this communication we present two new modifications of the benzidine stain. In method 1 we used as the main staining solutions, first, a mixture of benzidine and sodium nitroprusside in 50 per cent alcohol (not acidulated) and, second, a mixture of sodium nitroprusside and hydrogen peroxide in 50 per cent alcohol (acidulated with 2 per cent glacial acetic acid). Both solutions should be of a clear brownish color. The method is simple, and the blood vessels are outlined deep black. The stain can be completed within one-half hour. Application of heat and frequent shaking of the sections, as recommended by Pickworth, are not always necessary with this method. The exact procedure of method 1 follows.

METHOD 1

1. Fix the tissues in a 10 per cent concentration of solution of formaldehyde U. S. P. for from one to three weeks.
2. Cut frozen sections at from 200 to 300 microns.
3. Wash the sections thoroughly in distilled water for at least one-half hour.
4. Stain in solution A[7] for ten minutes.
5. Wash briefly in distilled water for ten seconds.
6. Stain in solution B[8] until the vascular pattern stands out black against a light background, placing the sections, if necessary, in an incubator at 37 C.
7. Wash in distilled water.
8. Dehydrate in 70 and 95 per cent alcohol (each acidulated with 2 per cent glacial acetic acid).
9. Dehydrate in absolute alcohol (not acidulated).
10. Complete dehydration in xylene.
11. Mount in balsam.

Sections after being well stained in solution A should present a yellowish appearance. When the sections are transferred to solution B, after being washed in

7. Solution A:
   Dissolve 0.5 gm. of benzidine in 50 cc. of absolute alcohol.
   Dissolve 0.1 gm. of sodium nitroprusside in 10 cc. of distilled water.
   Mix the two solutions and add distilled water to make 100 cc.

8. Solution B:

Absolute alcohol	50 cc.
Glacial acetic acid	2 cc.
Hydrogen peroxide 30 per cent	0.5 cc.
Sodium nitroprusside, dissolved in water	0.1 Gm.
Distilled water	to make 100 cc.

distilled water, the blood vessels as well as the background of the tissue at first appear bluish green; then the blood vessels gradually become black, while the background fades. Occasionally the entire section remains bluish at the end of twenty minutes. In such cases, the sections should be kept in solution B for a longer period, or placed in an incubator at about 37 C. until the contents of the blood vessels become black and the background fades out. This may take about twenty minutes longer.

Fig. 1.—Anterior central region of the cerebral cortex of a normal woman aged 40. Benzidine stain, method 1; enlargement, 27.

The alcoholic solution of benzidine which is used for making up solution A can be kept for at least one or two months without losing efficiency. The aqueous solution of sodium nitroprusside, however, deteriorates rapidly, especially if exposed to sunlight. This is evidenced by the formation of a greenish color when it is added to the solution of benzidine. Hence, it is necessary that the solution of sodium nitroprusside be freshly prepared each time it is to be used. After the sections are stained, they should be kept in the dark when they are not in use, because the sunlight bleaches them.

The success of the stain depends on the filling of the vessels with red blood cells. As pointed out by Pickworth, great care should therefore be taken to avoid loss of blood from the vessels at the time of removal and section of the tissues. Our best results were obtained with materials which had been fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. for from one to three weeks. However, satisfactory staining has been secured occasionally with tissues which have been kept in a 10 per cent concentration of solution of formaldehyde

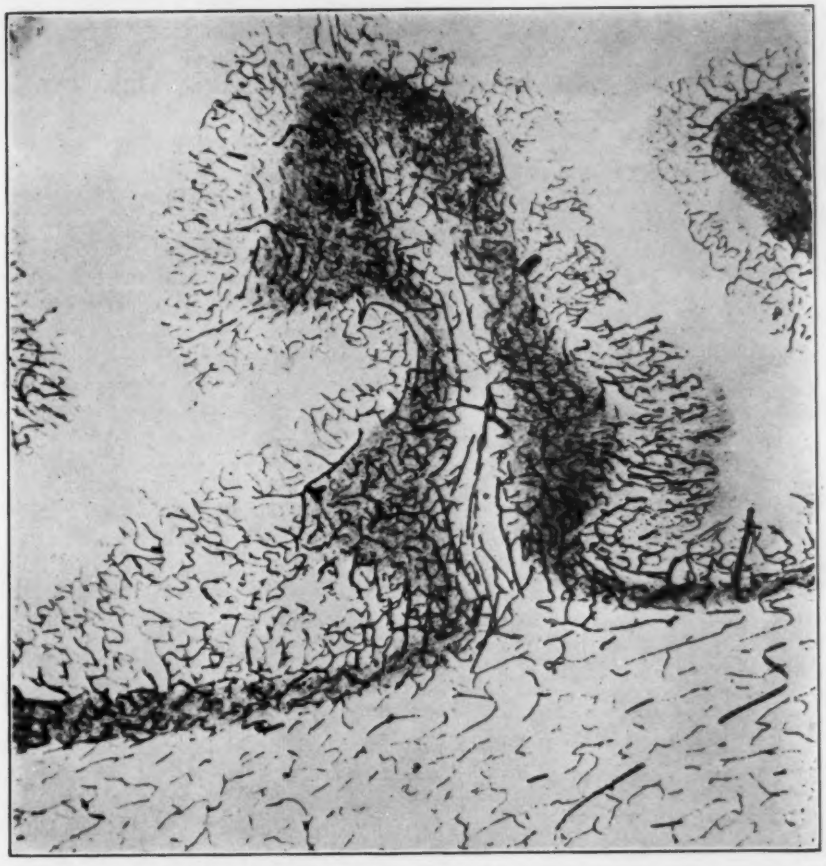

Fig. 2.—Cerebellar convolution from the brain of a normal woman aged 40. Benzidine stain, method 1; enlargement, 27.

U. S. P. up to six or eight months. The blood vessels in too old material, as a rule, do not take the stain well. On the other hand, material used for staining too early after fixation, that is, in less than one week after fixation, is also unsatisfactory, owing to a greenish or bluish coloring of structures other than the darkly stained blood vessels.

Since formaldehyde reacts with benzidine to form a white precipitate on the surface of the sections, thus interfering with the results of the staining, it is important to wash the sections in distilled water for at least a half-hour before placing them in solution A.

Discussion of the normal vascular pattern of the central nervous system is beyond the scope of this paper. However, for the purpose of illustrating the result with this new modification, we insert a picture of the cerebral (fig. 1) and another of the cerebellar cortex (fig. 2).

METHOD 2

This method, which is particularly well suited for examination of tissue soon after fixation, does not differ from the technic used by Campbell, Alexander and Putnam [5] except for the quantities of three of the chemicals used in making up the staining solutions. The procedure is as follows:

1. Cut sections at from 200 to 300 microns from material fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. for from three to fourteen days.
2. Wash sections for one-half hour after sectioning.
3. Place sections in solution A [9] for one-half hour at 37 C., and shake frequently.
4. Wash quickly in water.
5. Place sections in solution B [10] for one-half hour at 37 C., and shake frequently.
6. Wash, dehydrate, clear in xylene and mount in balsam.

SUMMARY

New modifications of the benzidine stain for study of the vascular pattern of the central nervous system are reported. The methods are simple. The blood contained in the vessels is stained black. The best results are obtained by method 1 with material which has been fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. for from one to three weeks, and by method 2 with material fixed in the same fixative for from three to fourteen days. Exposure to sunlight bleaches stained specimens; therefore they should be kept in the dark when they are not in use.

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9. Solution A:
   Dissolve 0.25 Gm. (2 knife points) of benzidine in 1 cc. of glacial acetic acid. Add 50 cc. of distilled water.
   Dissolve 0.1 Gm. of sodium nitroprusside in distilled water and add to the solution of benzidine. Mix and add water to make 100 cc. If precipitate forms, filter.
10. Solution B:
    Add 0.5 cc. of a 30 per cent solution of hydrogen peroxide to 100 cc. of distilled water.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following physicians were certified on June 11, 1938.

Without examination.—Psychiatry and Neurology: Rayford Kennedy Adams, Skillman, N. J.; Buell Leslie Ashmore, Des Moines, Iowa; Benjamin Thomas Burley, Worcester, Mass.; Francis Abbott Carmichael, Fulton, Mo.; Arthur H. Deppe, St. Louis; H. Douglas Eaton, Los Angeles; Harold C. Goodwin, Springfield, Mass.; Harold Inman Gosline, New York; Rossner E. Graham, Oakland, Calif.; Ernest M. Hammes, St. Paul; Ross D. Helmer, Utica, N. Y.; Charles Shute Holbrook, New Orleans; John Y. Notkin, Poughkeepsie, N. Y.; Aaron J. Rosanoff, Los Angeles; Simon Rothenberg, Brooklyn; Alexander H. Rubinowitz, New York; Walter Frank Schaller, San Francisco; Hyman D. Shapiro, Washington, D. C.; Edward F. Stadtherr, San Francisco; Arthur R. Timme, Los Angeles; Clarence Morton Trippe, Asbury Park, N. J.; Edward W. Twitchell, San Francisco; N. W. Winkelman, Philadelphia.

Psychiatry: E. Armitage Baber, Cincinnati; Leon E. Duval, Ionia, Mich.; Annie R. Elliott, Norristown, Pa.; James S. Hammers, Lancaster, Pa.; Hugh C. Henry, Petersburg, Va.; Ralph Lee Hill, Wernersville, Pa.; Harry F. Hoffman, Allentown, Pa.; Salomon Katzenelbogen, Baltimore; Olga Knopf, New York; Elizabeth McLaughry, New Wilmington, Pa.; Martin W. Peck, Boston; Sandor Rado, New York; Perry C. Robertson, Ionia, Mich.; James W. Vernon, Morganton, N. C.; M. Mortimer Sherman, Brooklyn; Edson Hun Steele, Los Angeles; Erwin Wexberg, New Orleans.

Neurology: Ransom A. Greene (complementary), Waverley, Mass.

By Examination.—Psychiatry and Neurology: Herman Chor, Chicago; George S. Johnson, San Francisco; Richard De Monbrun Kepner, Honolulu, Hawaii; Joseph A. Luhan, Chicago; Pearl Sylvia Pouppirt, San Francisco; George Noel Ruhberg, St. Paul; Melvin Ralph Somers, San Francisco; Eugene Ziskind, Los Angeles.

Psychiatry: Burton W. Adams, Oakland, Calif.; Ralph S. Banay, New York; Wendell H. Hutchens, Portland, Ore.; Frederick Lemere, Seattle; Juul C. Nielsen, Ingleside, Neb.; Ernest F. Russell, Santa Barbara, Calif.; William Lyall Valens, Compton, Calif.

AMERICAN COLLEGE OF PHYSICIANS

The twenty-third annual session of the American College of Physicians will be held in New Orleans, March 27 to 31, 1939, with general headquarters at the Municipal Auditorium. Dr. William J. Kerr, of San Francisco, is president of the college and will have charge of the program of general scientific sessions. Dr. John H. Musser, of New Orleans, has been appointed general chairman of the session and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of round table discussions to be conducted at the headquarters.

DIRECTOR OF LABORATORIES AND RESEARCH, ST. ELIZABETHS HOSPITAL WASHINGTON, D. C.

Solomon Katzenelbogen, M.D., has been appointed director of laboratories and research at St. Elizabeths Hospital, Washington, D. C., effective July 15, 1938. Dr. Katzenelbogen has been associated with the Henry Phipps Psychiatric Clinic in Baltimore since 1928 and is at present associate professor of psychiatry at Johns Hopkins University Medical School.

Abstracts from Current Literature

Physiology and Biochemistry

CHEMICAL STUDIES ON THE NEUROPROTEINS: III. AN INDICATION FOR SEX DIFFERENCES IN THE AMINO ACID COMPOSITION OF PRIMATE BRAIN PROTEINS. RICHARD J. BLOCK, J. Biol. Chem. **121**:411, 1937.

Proteins prepared from the brains of five human and two monkey males and from three human and three monkey females were analyzed for nitrogen, histidine, lysine, arginine, tyrosine and tryptophan. The amino-acid composition of neuroproteins for male and those for female primates appear to be approximately the same, except for lysine, which is present in somewhat larger amounts in the brain proteins of males. Thus, the average molecular ratio of lysine to arginine is 100:83 for males and 100:93 for females. PAGE, Indianapolis.

THE CARBOHYDRATE METABOLISM OF BRAIN: V. THE EFFECT OF CERTAIN NARCOTICS AND CONVULSANT DRUGS UPON THE CARBOHYDRATE AND PHOSPHOCREATINE CONTENT OF RABBIT BRAIN. STANLEY E. KERR and ALBERT ANTAKI, J. Biol. Chem. **122**:49, 1937.

Excitation of the central nervous system of rabbits to an extent sufficient to cause convulsions by drugs such as strychnine, picrotoxin and cardiazole is not regularly associated with any significant change in glycogen, free sugar or lactic acid. Phosphocreatine also remains unchanged. These experiments do not support those of Asher and Takahashi (*Proc. Soc. Exper. Biol. & Med.* **22**:238, 1925) or Uchida (*Biochem. Ztschr.* **167**:9, 1926). PAGE, Indianapolis.

NOTE ON THE PHOSPHORUS CONTENT OF RAT BRAIN IN EXPERIMENTAL RICKETS. STANLEY E. KERR, J. Biol. Chem. **122**:53, 1937.

Kerr has reinvestigated the work of Hess, Gross, Weinstock and Berliner (*J. Biol. Chem.* **98**:625, 1932), who reported the finding of lowered contents of inorganic phosphate and calcium in the rat brain as a result of experimental rickets. Kerr found no change from the normal in inorganic phosphorus, phosphocreatine phosphorus, undetermined acid-soluble phosphorus, total acid-soluble phosphorus, total phosphorus and nucleotide nitrogen. Phosphocreatine and acid-insoluble (lipid) phosphorus were consistently lower in brains of rachitic animals, but the differences from normal were small. PAGE, Indianapolis.

THE IRON, COPPER AND MANGANESE CONTENT OF THE HUMAN BRAIN. A. H. TINGEY, J. Ment. Sc. **83**:452 (July) 1937.

All forms of iron and copper are about evenly distributed throughout the cortex, white matter and cerebellar cortex. A large excess of all forms of iron and manganese was noted in the corpus striatum. The highest concentration of iron was found in the pallidum and substantia nigra. Thus, in the corpus striatum the total amount of iron was 55 mg. per hundred grams of tissue, whereas in the cortex it was 22 mg. A large excess of copper was found in the substantia nigra. The concentration of iron was much higher in the cortex of persons with dementia paralytica.

Children up to the age of 11 have less iron than adults. On the other hand, copper and manganese reach approximately the adult level at the age of 2 years.

In children the iron, copper and manganese levels fall during nursing and begin to increase during childhood. The average copper content of the brain varies from 0.43 to 0.6 mg. per hundred grams of tissue. Manganese varies from 0.019 to 0.053 mg.

KASANIN, Chicago.

Neuropathology

POST-TRAUMATIC INTERNAL HYDROCEPHALUS. ALAN R. MORITZ and WILLIAM B. WARTMAN, Am. J. M. Sc. **195**:65 (Jan.) 1938.

Moritz and Wartman report four cases in which there were a history of trauma followed by a period of unconsciousness and a latent period of variable duration between the accident and the onset of symptoms of internal hydrocephalus. The intervals between the injury to the head and death varied from three and one-half months to eight years. The outstanding symptoms were stiffness of the neck, lethargy, headache and vomiting. In all the cases autopsy showed partial or complete fusion of the pia-arachnoid in the region of the fourth ventricle due to fibrous adhesions which were infiltrated with lymphocytes and large macrophages containing hemosiderin. Thus, the acquired internal hydrocephalus was due to adhesions in the region of the fourth ventricle. That the adhesions contained intracellular and extracellular hemosiderin indicates that they resulted from the organization of a hematoma or a hemorrhagic exudate.

MICHAELS, Boston.

THE PRIMARY MELANOMAS OF THE LEPTOMENINGES. MAX T. SCHNITKER and DARRELL AYER, J. Nerv. & Ment. Dis. **87**:45 (Jan.) 1938.

Melanin occurs normally not only in the skin, iris, ciliary body, choroid and retina of the eye and chromaffin tissue of the adrenal gland and carotid body but in the substantia nigra and the pia mater. In the pia, collections of melanin are seen most commonly in the depths of the sulci, over the base of the brain, in the anterior median fissure and between the ventral and dorsal roots of the spinal cord, especially in the thoracic and lumbar enlargements. It also occurs in the olfactory epithelium and in the labyrinth. Metastatic melanomas in the brain and spinal cord arising from a primary growth in the skin are fairly common, but primary melanomas of the nervous system are rare. Schnitker and Ayer review the literature on primary melanomas of the central nervous system from 1859, when Virchow reported the first instance. Of thirty cases recorded, all occurred in white persons, twenty in males and ten in females. The highly variable symptoms and signs have not led to a correct diagnosis during life, although tumor of the brain has been diagnosed in ten cases. Examination of the spinal fluid, made in only fourteen instances, showed increase in pressure in five cases and spinal subarachnoid block in two. The number of lymphocytes varied from none to 63 per cubic millimeter, but tumor cells were not observed. The tumors occurred predominantly in the areas of normal pial pigmentation; they were observed chiefly along the base of the brain, frequently involving the cranial nerves and spreading fanwise over the inferior surface of the temporal lobes, the upper and lower surfaces of the cerebellum and in the major sulci of the hemispheres. When the spinal cord was involved, the dorsal and lateral aspects of the lower thoracic segments were most frequently pigmented. The tumor was usually widely spread in nodules of varying size, though larger aggregations, from 1 to 5 cm. in diameter, sometimes occurred. Schnitker and Ayer report a case of primary melanoma of the meninges in a white woman aged 49. No tumor or pigmentation was observed in the skin or mucous membranes of any part of the body. Microscopic examination of a tumor removed from the spinal canal during life revealed large fusiform acidophil cells with ovoid nuclei, finely granular cytoplasm and extremely rare mitotic figures. These were arranged in sweeping interlacing sheaves. There was no evidence of intercellular substance or fibrils. Round droplets of brown refractile pigment were seen lying free or in macrophages, and sometimes in the cytoplasm of the tumor cells. Autopsy revealed that the surface of the brain was studded

with deep black, confluent plaques, aggregated for the most part over the base of the brain but extending over the whole cerebellum and, to a lesser extent, over the lateral aspects of the cerebral hemispheres. This distribution of the tumors corresponded in general to that of the normal pial pigmentation. The tumor cells invaded many of the cranial nerves at the base of the brain, as well as the superficial layers of the cortex of the cerebrum and cerebellum. The leptomeninges of the entire spinal cord and cauda equina were densely infiltrated with the tumor. The cells of the tumor were packed with small dark brown or black granules which gave the staining reactions of melanin. There was a metastatic nodule of the melanoma in the liver, and argyrophil granules were observed in the cells of the renal tubules and the submucosa of the colon.

Schnitker and Ayer emphasize the theory that melanin cells are closely related to cutaneous tactile end-organs. The blastomeric origin of the melanoblasts and of the meninges themselves is still in dispute, and may be both ectodermal and mesodermal.

MACKAY, Chicago.

THE LAURENCE-MOON-BIEDL SYNDROME. G. M. GRIFFITHS, J. Neurol. & Psychiat. **1**:1 (Jan.) 1938.

Griffiths reports the case of a girl aged 5 years with manifestations of a Laurence-Moon-Biedl syndrome. The symptoms consisted of obesity, mental retardation, retinitis pigmentosa with squint and nystagmus and symmetric polydactyly and syndactyly of the feet. There was a familial trend toward a similar disorder. Some clinical improvement followed treatment with extract of whole pituitary, but the child died of an intercurrent attack of measles. Necropsy disclosed: developmental defects of the skeleton and kidneys, and probably of the eyes; hypoplasia of the thymus, and abnormally small gonads. The pituitary body was very small, and there was a large proportion of basophil cells in the anterior lobe. Examination of the brain disclosed slight macroscopic atrophy of the frontal lobes, but no histologic changes. There was paucity of cells in the tuberal nuclei, but no other definite changes in the hypothalamus. Some of the symptoms and the changes in the pituitary gland suggested analogy with the syndrome of pituitary basophilism. Griffiths emphasizes the genetic aspect of the syndrome and agrees with the view of L'hermitte and Bollack that the disorder is due to a germinal disturbance.

N. MALAMUD, Ann Arbor, Mich.

AN EXAMPLE OF STATUS MARMORATUS OF THE CEREBRAL CORTEX. R. M. NORMAN, J. Neurol. & Psychiat. **1**:7 (Jan.) 1938.

One of the chief problems in the study of the condition known as status marmoratus concerns the pathogenesis of the hypermyelinated plaques. Whereas the abnormal production of myelin is believed to be due to perversion of glial function, the mode of origin of the abundant axis-cylinders remains unknown. Norman reports a case of status marmoratus, which involved the cerebral cortex and the putamen, in an adult epileptic idiot. In addition, there was a complex combination of malformed (microgyric) and atrophic (ulegyric) gyri in the parietal and occipital lobes. This consisted of several small gyri developed on one parent stem, with malformed bulbous crowns and atrophic changes in the walls and basal portions. The malformed crowns contained dense whorls of diffuse hypermyelination, abundant axis-cylinders and fine gliosis; the atrophic basal parts disclosed demyelination with few axis-cylinders and dense gliosis. In the cortex of the adjacent larger gyri there was a similar distribution of a dense network of axis-cylinders showing no signs of regeneration and fine gliosis in areas of typical retiform status marmoratus, whereas the central cores were composed of dense gliosis and few axis-cylinders. On the basis of these changes, Norman concludes that the abnormal development of axis-cylinders in status marmoratus is not a regenerative phenomenon but is explained by a process akin to the "compensatory collateral hypertrophy of Cajal." According to Cajal, section of the axon of a pyramidal cell distal to the origin of the initial collaterals results in compensatory

hypertrophy of the collateral branches. With regard to the interpretation of his case, Norman is of the opinion that both the malformation and the atrophic changes can be attributed to the same pathologic process acting on the cerebral cortex during an early stage of development.

N. MALAMUD, Ann Arbor, Mich.

THE PATHOLOGY OF APOPLEXY. K. STERN, J. Neurol. & Psychiat. **1**:26 (Jan.) 1938.

In a brief summary of the various concepts and problems concerning apoplexy, Stern emphasizes that three types of lesions form the anatomic basis of cerebral apoplexy: (1) massive hemorrhage, (2) softening and (3) hemorrhagic infarction. They are frequently confused in the literature. The earliest views with regard to the pathogenesis of cerebral hemorrhage were purely mechanical; namely, rupture of miliary aneurysms (Charcot and Bouchard) or local dilatation of normal vessels (Pick and others). This theory was later rejected by Rosenblath, who expressed the opinion that acute necrosis of numerous vessels and of the surrounding brain tissue is the primary event, preceding and determining the expansion of the hemorrhage. Although this view of the mechanism of the lesion has been generally accepted, Rosenblath's postulation of a chemotoxic etiology of the acute necrosis has been refuted. Current opinion is based on the theory of Westphal and Bär that the necrosis preceding the hemorrhage is produced by arteriospasm. This concept of transient "functional" or "vasomotor" disturbances has accordingly replaced the classic mechanical views. However, although the production of softenings may thus be accounted for, the theory does not offer an adequate explanation for the production of hemorrhage. Moreover, there is no actual evidence that angiospasm can produce necrosis of the vessel or of the tissue. Ricker's experimental demonstrations that hemorrhagic and ischemic infarctions result not from angiospasm but from prestasis and stasis are more scientifically founded, although they do not apply strictly to the human brain. The views of Ricker, however, fail to account for the manner in which hemorrhages are produced. According to the experiments of Lampert and Müller, a sudden increase in intra-arterial pressure fails ordinarily to produce rupture of the vessel and hemorrhage. The strict localization of hemorrhages is attributed by Ricker and Schwartz to pathologic stimuli to the arterial trunk, released by a nerve mechanism and resulting in circulatory disturbances in the terminal distribution of the vessel. One would expect then, since such stimuli follow the most direct stream of the blood, that hemorrhages would be more frequent in the hypothalamus than in the basal ganglia or pons. The reverse, however, occurs. As a reaction to the inadequacies of these views, investigators have recently returned to the classic mechanical concepts.

The problem of local vulnerability, such as predilective sites for apoplectic hemorrhage, requires further investigation. In order to explain this it is necessary to find a common feature in the vascular supply of all the vulnerable regions, on the one hand, and that of the resistant parts, on the other. Various factors have been mentioned, such as extracerebral and intracerebral anastomoses, developmental anomalies of the vessels and the effects of increased intracranial pressure.

Stern is of the opinion that further research is necessary not only on the physiologic phenomena of the intracranial circulation but on the normal anatomic relations of the cerebral vessels, particularly the intracerebral veins, as well as their embryologic development.

N. MALAMUD, Ann Arbor, Mich.

DIFFUSE WHITE MATTER GLIOSIS IN MENTAL DEFECTIVES. A. MEYER and I. C. COOK, J. Ment. Sc. **83**:258 (May) 1937.

Meyer and Cook studied the brains of seven low grade mentally defective persons with gross neurologic lesions, six microcephalic patients with spastic diplegia, two able-bodied microcephalic patients, one idiot and six patients with

mongolism. In all cases there was constant, striking proliferation of the fibrous glia cells, in both the cerebrum and the cerebellum. In many cases the cortical changes were not as marked as the lesions of the white matter. In none was demyelination a striking feature; its severity did not approach that of the glial proliferation. The gliosis was either diffuse or patchy, and was often perivascular.

The pathogenesis of the gliosis is obscure. There is evidence which suggests that a vascular factor or defective tissue oxygenation from some other source may be the immediate cause of the change in many cases. No conclusions can be drawn concerning the role of the glial changes in the production of mental deficiency.

KASANIN, Chicago.

LESIONS OF THE BRAIN IN DOGS WITH AN ECK FISTULA. N. FIESSINGER, L. CORNIL, Y. POURSINES and J. PAILLAS, Ann. d'anat. path. **14**:553, 1937.

The observations at autopsy on two dogs with an Eck fistula are reported. One had survived for six days, and the other, for fifty-six days after the operation. In the first case the only lesions of the brain were generalized capillary stasis and mild proliferation of oligodendrocytes in the white matter. In the second case a short period of feeding meat had produced transitory paresis of the hindlimbs; at death, the body had lost about half its weight; the liver was atrophic and yellowish and showed fatty degeneration with peripheral cirrhosis. Histologic examination of the brain revealed mild round cell infiltration of the pia-arachnoid, together with numerous capillary hemorrhages. Except for scattered, mild perivascular small round cell infiltrations, the cortex appeared normal. The white matter, as in the first case, showed proliferation of oligodendrocytes and perivascular hemorrhages. The subependymal tissue was edematous; here, too, perivascular cellular infiltration and proliferation of glia cells were present. The authors speak of "diffuse leuko-encephalosis" as the characteristic cerebral lesion in dogs with an Eck fistula.

WEIL, Chicago.

Psychiatry and Psychopathology

CLINICAL FEATURES AND TREATMENT OF FUNCTIONAL OR NERVOUS VOMITING: REPORT OF 140 CASES. D. L. WILBUR and R. N. WASHBURN, J. A. M. A. **110**:477 (Feb. 12) 1938.

Wilbur and Washburn discuss the clinical data in 140 cases of functional vomiting, in 97 of which they obtained reports of observations on the results of treatment covering a period of from two to eight years after examination. Of the 140 patients, 112 were females and 28 males; 89 patients were between the ages of 20 and 40. Vomiting is a symptom and not a disease, and it occurs in a large variety of conditions. The causes of vomiting were classified by Hurst as local, reflex, toxic and central; under appropriate circumstances, any variety of nonhysterical vomiting may be perpetuated and exaggerated by suggestion after its original cause has disappeared. Local causes of vomiting include irritation or disease of the stomach, and reflex causes are represented by appendicitis, cholecystic disease, pregnancy and seasickness. Vomiting of toxic origin occurs during acute infections, whereas vomiting of central origin may appear in the course of cerebral disease or as an expression of extreme emotional disturbance or anxiety. If vomiting occurs as a result of one of these abnormalities in the case of a person who is nervously unstable or neurotic, it is possible that it may continue and become a nervous habit. The diagnosis of functional vomiting is generally not difficult. The typical picture is presented by a relatively young woman with signs of nervous, emotional or cardiovascular instability who, without much apparent reason or associated abdominal distress or nausea, has for months or years vomited within an hour after meals, without appreciable effect on her general health. Another feature which may be helpful in diagnosis is the onset or recurrence of vomiting during periods of nervous stress or strain or as a result

of fatigue. The ability or desire to eat again immediately after vomiting is characteristic in many cases of functional vomiting; it is rarely present when vomiting is the result of organic disease. The methods of treating functional vomiting vary widely and include all the known methods of treating neurotic patients. In the final analysis, psychotherapy is of tremendous importance. Many patients require little more than the reassurance that they do not have an organic disease. In other cases, such reassurance and a careful explanation of the factors and mechanisms involved in producing the bouts of vomiting by a physician in whom the patient has great confidence are sufficient to overcome the difficulty. Mild sedatives, particularly bromides and barbiturates, given a short time before meals, and a dry diet are extremely useful. In many of these cases the stomach is apparently better able to handle solid than liquid food, and solid food given without liquid is much more difficult to regurgitate or vomit. Adequate rest, mental and physical relaxation, exercise, physical therapy and similar procedures may be of great benefit indirectly in improving the nervous state of the person with functional vomiting and may aid him in overcoming his symptoms. In some cases in which vomiting is marked and has led to much loss of weight and malnutrition, or in which the nervous features are outstanding, hospital treatment may be advisable. Fifty per cent of the 97 patients who were followed for from two to eight years after examination had complete relief from vomiting.

EDITOR'S ABSTRACT.

THE CLINICAL EFFECTS OF BENZEDRINE SULPHATE IN MENTAL PATIENTS WITH RETARDED ACTIVITY. LAWRENCE F. WOOLLEY, Psychoanalyt. Quart. **12**:66 (Jan.) 1938.

Woolley reports the results of investigation of the stimulating effect of benzedrine on retarded behavior in certain types of functional psychoses. He selected 70 patients under 50 years of age for his study. In 44 cases the diagnosis was schizophrenia; in 21, manic-depressive psychosis, and in 5, psychoneurosis. All the patients had been in practically the same condition for a considerable time prior to the investigation. Twenty-four hour behavior charts were started before the actual experiments took place and were continued throughout the investigation. Benzedrine sulfate, in aqueous solution, was given in doses of from 10 to 60 mg. In order to exclude as much as possible the suggestive influence of the procedure, the experiments were initiated and interrupted from time to time by the administration of a substitute solution. Of the schizophrenic patients, 2 (4 per cent), with the catatonic type, recovered; 10 (23 per cent) showed improvement; 21 (48 per cent) were not benefited, and 11 (25 per cent) became worse. Of the manic-depressive patients, 1 (5 per cent) recovered; 3 (14 per cent) showed improvement; 14 (67 per cent) were not benefited and 3 (14 per cent) became worse. Of the psychoneurotic patients, 1 showed improvement; 3 were not benefited, and 1 became worse. Woolley believes that without benzedrine "therapeutic access to these patients would have been long delayed." Among the unfavorable responses, he draws attention to the incidence of anxiety and panics precipitated in "tense or agitated, depressed or catatonic individuals." One serious suicidal attempt occurred. Some of the patients showed a striking rise in blood pressure, and 1, a slight decrease. Woolley is unable to draw important general conclusions from his investigation. In general, it can be said that if 10 mg. of benzedrine sulfate does not produce signs of favorable response practically immediately, there is little hope of good results. It is not possible to predict what patients are likely to react favorably, although those who showed "agitation or fear and anxiety" seemed to have a poorer prognosis for benefit from treatment than the others. The concurrent pharmacodynamic tests indicated that the predominance of vagotonic or of sympathicotonic reactions did not matter with regard to the outcome. Woolley, in considering the variability of effects and the unpredictability of the treatment, regards of interest the fact that normal persons who received from 10 to 20 mg. of benzedrine sulfate showed a variability in responses comparable with those of the psychopathic patients.

ANTHONISEN. Boston.

IMPOTENCE. ADRIEN STEPHEN, Brit. J. M. Psychol. **15**:305, 1936.

The urinary function in children becomes associated with aggression. This is an important factor in the development of impotence, for "there is no doubt that it is the conflict between aggressive impulses that are normally expressed by urination and the loving impulses that are normally expressed by coitus that leads to impotence." The same association occurs between suckling and defecation. These early experiences of childhood which are centered around the mother establish the ambivalence which later creates the split in feeling leading to impotence. Physical expressions of love may also become those of hate. Sexual potency may be inhibited, therefore, by the unconscious fear either of retaliation by the hated object or of injuring and losing the loved object. In either instance impotence follows. This fundamental struggle between the aggressive, hostile and the tender, loving emotions seems to operate in the female as well as in the male.

ALLEN, Philadelphia.

AN INQUIRY INTO THE INCIDENCE OF "NEUROPATHIC" CONDITIONS IN THE RELATIVES OF NORMAL PERSONS. J. Ment. Sc. **83**:247 (May) 1937.

In order to ascertain the frequency of "neuropathic" disturbances among the relatives of normal persons, the Mental Deficiency Committee of the Royal Medico-Psychological Association distributed 1,500 questionnaires among the members of the staff, physicians, nurses and attendants at various hospitals for mental disease. Of these, 415 were returned complete. Of the 415 informants, 235 (57 per cent) reported one or more relatives with serious neurologic or mental disease. This figure is probably lower than the true percentage, since nurses with a bad family history frequently refused to fill out the questionnaire.

Furthermore, information was not sought about all the possible relatives; only direct relatives, such as children, parents, uncles, aunts, nephews and nieces, were included. After these facts are taken into consideration, there can be little doubt that the incidence of a positive family history of nervous or mental disease in the normal population must be at least 57 per cent. Families with abnormal persons are no larger than others.

KASANIN, Chicago.

RELATION BETWEEN HEREDITARY EPILEPSY AND MANIC-DEPRESSIVE PSYCHOSIS. N. BONDAREFF, Encéphale **31**:343, 1936.

In spite of the contradictory findings of Pierre Marie, Claude and others, Bondareff believes that hereditary epilepsy exists. He reports cases of epilepsy in four successive generations. In nine cases the offspring of parents with cyclophrenia either had epilepsy alone (three cases) or cyclophrenia associated with epilepsy (six cases). In the cases in which epilepsy was associated with cyclophrenia, the epileptic seizures occurred either during emotional agitation or independent of it. On the other hand, epilepsy has never been encountered among the ascendents of cyclophrenic persons. Dipsomania is considered homologous to cyclophrenia, as, during the years of prohibition in Russia Ossipoff observed depressions in dipsomaniac patients deprived of alcohol. Bondareff concludes that cyclophrenia is a complex disturbance which can be manifested either in prolonged attacks (manic-depressive psychosis or dipsomania) or in brief seizures (epilepsy).

LIBER, New York.

REMISSIONS IN SCHIZOPHRENIA: FREQUENCY AND DURATION BEFORE INSULIN THERAPY. L. FROMENTY, Encéphale **1**:274, 1937.

Authors who have reported favorable results from insulin therapy in schizophrenia have stated that the number of remissions is much greater than the incidence of spontaneous remissions. No statistical comparisons have been made to test this point. Fromenty chose for analysis 271 cases in which the diagnosis of schizophrenia was certain and in which complete data were obtainable. Some

of the patients had undergone various forms of treatment during the past ten years. The older patients were observed during the "nihilistic" or pretherapeutic period. None had received insulin. In 190 the disease evolved toward dementia with no remission; in 40, toward dementia with a variable number of remissions. In 41 there were complete and lasting remissions, of six to ten years' duration.

LIBER, New York.

HYSTERICAL SENSORY DISTURBANCES: ROLE OF CONDITIONED REFLEXES IN PHYSIOPATHOLOGIC BASIS OF HYSTERIA. G. MARINESCO, Rev. neurol. **68**:585, 1937.

Marinesco reports a case in which he had made a diagnosis of hysteria which Froment had contested. This report attempts to demonstrate the correctness of the diagnosis and to answer Froment's criticism of Marinesco's ideas concerning hysteria (*Rev. neurol.* **66**:587 [Nov.] 1936; **67**:153 [Feb.] 1937). A woman had total left hemianesthesia to all forms of sensation, which had lasted for several years. After a dream that a well known surgeon had operated on the left side of her head, the anesthesia disappeared from the face. Later, after several sessions of faradization, sensation returned to the trunk and, during high fever, with a temperature of from 38.5 to 39.5 C. (101.3 to 103.1 F.), to the involved extremities, leaving only a small zone of anesthesia on the forearm. A number of tests were performed to show the reality of the anesthesia. Boiling water on the palm of the hand was not perceived; the hand was not withdrawn, although the water was applied long enough to result in a large bleb. Painful stimulation of the normal side of the body resulted in tachycardia and marked changes in respiration, while the pulse and respiratory rates remained unchanged when the same stimuli were applied to the anesthetic side. In like manner, oscillometric and plethysmographic changes, present on stimulation of the normal side, were absent on stimulation of the anesthetic side. Conditioned reflexes, in which the response was a plethysmographic variation indicating vasoconstriction, were readily produced in this patient. Marinesco had previously shown that conditioned reflexes are easily formed and are tenacious in hysterical patients. Nevertheless, while conditioned vasoconstriction, in which the absolute stimulus was a pin prick and the conditioned stimulus tactile, was produced in the normal extremities after twelve repetitions of the combination, no conditioning resulted from stimulation of the anesthetic side, even after fifty-six combinations. The psychogalvanic reflex, present when the normal side was stimulated, was absent when the anesthetic side was stimulated. The carotid sinus reflex was of slight amplitude; according to previous work by Marinesco and Kreindler, this also occurs in hysteria. Recently, Marinesco, with Sager and Kreindler, has observed electro-encephalographic currents of only 35 microvolts in persons with hysteria, as compared with an average of 100 microvolts in normal persons. Marinesco concludes that hysterical hemianesthesia is "a physiopathologic reality whose characteristics can be determined by incontestable objective methods."

LIBER, New York.

CONVULSIONS AND INSULIN TREATMENT. F. GEORGI, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:49, 1937.

Georgi reports the results of comparative humoral studies on the effects of large doses of insulin and of convulsive doses of metrazol. Repeated estimations of the sugar content of the blood were made for 5 schizophrenic patients receiving insulin treatment, from ten to fourteen readings being made in each case on the same day of each successive week. The most rapid fall in blood sugar was found to occur during the first thirty minutes after injection of insulin, although no hypoglycemic symptoms were observed during this period; regardless of the dose of insulin, the lowest, or close to the lowest, level was usually reached during the third half-hour after injection. Even without the administration of carbohydrates, the sugar content of the blood began to increase during the second hour or at the

beginning of the third hour. Although light somnolence, sweating and epileptiform phenomena were seen earlier, sopor and coma first appeared either when the blood sugar had reached its lowest level or when it had passed this point and had begun to increase. The relation between hypoglycemic symptoms and the time interval seemed particularly noteworthy. Regardless of the dose of insulin, provided that it was adequate, the individual patient tended to show the same symptoms day after day, and at approximately the same period after injection. It was also observed that a part of the dextrose administered intravenously to terminate the reaction tended to disappear rapidly from the blood.

Georgi expresses the view that during the first sixty or ninety minutes after injection of insulin, a period during which there are no serious hypoglycemic symptoms, sugar passes from the blood into the tissues; further, that in the course of the second hour a definite turning point is reached. Up to this point the ganglion cells either are storing sugar or at least are not losing an appreciable amount, while the body fluids are being deprived of sugar. This "increased potential" enhances the irritability of the cells and accounts for the convulsive phenomena observed during this period. Coma supervenes after the process has been reversed and the cerebral ganglion cells are being deprived of the sugar which is passing back into the blood. After administration of carbohydrates, dextrose again passes into the tissues from the blood, and during this period further convulsive attacks may occur. That cells deprived of sugar do not utilize oxygen effectively is demonstrated by the slight difference in color between the venous and the arterial blood removed during coma.

The observation that certain patients who were not benefited by insulin therapy and who, furthermore, did not have convulsions during this treatment responded promptly to convulsions induced by intravenous injections of metrazol prompted humoral studies on patients receiving the latter treatment. Seventeen schizophrenic patients received altogether 262 injections of metrazol and, as a result, had 153 major and 21 minor seizures. Blood was removed before injection, during the few seconds of the preparoxysmal phase, during the attack and in the postparoxysmal period. A marked change in the sugar concentration of the blood, amounting to as much as 45 mg. per hundred cubic centimeters, was constant; this consisted in either an increase or a decrease during the preparoxysmal phase, followed always by a change in the opposite direction during the convulsion. A marked postparoxysmal rise to 75 mg. per hundred cubic centimeters was also constant. Similar, but quantitatively much less pronounced, changes were observed when a seizure did not occur. There was a simultaneous disturbance of the equilibrium between the concentration of potassium and that of calcium in the blood, consisting of an increase in potassium and a decrease in calcium. The quotient fell during the intraparoxysmal phase, to rise again after the convulsion. The sedimentation rate slowed progressively during the three phases, whereas the plasma lability increased, indicating a disturbance in ionic equilibrium. When a convulsion failed to supervene, the plasma lability remained unchanged, while the sedimentation rate increased slightly. Leukocytosis was demonstrated during the convulsions. Schilling counts revealed a shift to the right in the preparoxysmal and intraparoxysmal phases, followed by a definite shift to the left after the seizure. The pulse pressure was increased during the attack.

Georgi expresses the belief that the two therapeutic procedures have two main points in common: They bring about irritation of the cell membrane, and they increase its permeability. He refers, in this connection, to the decreased permeability of the barrier between the blood and the cerebrospinal fluid, which has been demonstrated in cases of schizophrenia of long standing. A combination of the two treatments seems desirable on practical, as well as theoretic, grounds, since patients in the hypoglycemic state not only show much less than the usual dread of the impending convulsion but have convulsions with greater regularity and with smaller doses of metrazol.

DANIELS, Denver.

Diseases of the Brain

VITAMIN DEFICIENCY AS ETIOLOGIC FACTOR IN CENTRAL NEURITIS. D. J. SULLIVAN and A. SIMON, M. Bull. Vet. Admin. **14**:228 (Jan.) 1938.

The picture of central neuritis described by Meyer is a terminal state, and Sullivan and Simon believe it to be the result of prolonged avitaminosis, particularly vitamin B_1 deficiency. No abnormalities are observed grossly in the brain. The microscopic changes involve the ganglion cells of the brain and spinal cord. The picture is characterized by central chromatolysis, lateral displacement of the nucleus and swelling of the cell body. These changes are most marked in the large and medium size pyramidal cells of the cortex, the oculomotor nucleus, the nucleus ambiguus, the ventral horn motor cells and perhaps the lateral horn cells. The neuropathologic changes are of a degenerative type, so that the term "central neuritis," which suggests inflammation, is a misnomer. "Central neuritis" occurs in a variety of conditions, such as Korsakoff's psychosis, pellagra, alcoholic polyneuritis, alcoholic encephalopathy, polyneuritis of pregnancy and acrodynia. Toxins and infections are not the primary etiologic factor in the causation of this syndrome. Vitamin deficiency is the etiologic basis of this disorder, and apparently lack of vitamin B_1 is the essential factor. A diet high in vitamins with administration particularly of vitamin B_1 (antineuritic) is indicated therapeutically. Three cases with clinicopathologic data are described. EDITORS' ABSTRACT.

HYPOGLYCEMIA AS CAUSE OF SEIZURES IN GENERAL PARALYSIS. L. BIRNBAUM and J. A. WOOD, M. Bull. Vet. Admin. **14**:236 (Jan.) 1938.

Birnbaum and Wood studied the sugar tolerance curves for nine patients with dementia paralytica who had seizures. Abnormal curves and sharp drops in hypoglycemic levels were observed in all cases. The average difference between the highest and the lowest sugar levels for these patients was much greater than that for the subjects used as controls. Three patients had symptoms of seizures while the blood sugar was at a hypoglycemic level; these symptoms cleared as the level of the blood sugar rose. Therapy was attempted with one patient whose frequent seizures made him a suitable subject. A high fat, low carbohydrate (ketogenic) diet resulted in an increased number of seizures. Intramuscular injections of extract of anterior pituitary in varying doses (with the patient on a normal diet) caused a reduction in the number of seizures, from an average of thirty to one of fifteen a week. A 25 per cent solution of dextrose given intravenously in a dose of 40 cc. to a patient who was having a series of seizures resulted in immediate cessation of the attacks. The seizures had some relation to altered sugar metabolism in these patients. AUTHORS' ABSTRACT.

LIPOMA OF THE CORPUS CALLOSUM. G. GANDER, Ann. d'anat. path. **14**:513, 1937.

Gander adds a case of lipoma of the corpus callosum to the twenty-three instances reported previously. The tumor was attached to the upper surface of the splenium and invaded the choroid plexus of the lateral ventricle. He regards the lipoma as a malformation of the primitive pia-arachnoid. WEIL, Chicago.

MECHANISM OF DEATH IN CERTAIN CASES OF CEREBRAL TUMOR. PAUL VAN GEHUCHTEN, Encéphale **1**:113, 1937.

Death followed lumbar puncture, ventriculography or decompressive craniotomy in five cases of tumor of the temporal lobe and in one of tumor of the occipital lobe. The tumor was a glioblastoma in two cases, an ependymoglioma in one and a meningioma in one; the variety was not stated in two cases. In all cases the medial portion of the temporal lobe on the side of the tumor was pushed down beside the midbrain, which was markedly compressed. Diapedetic hemorrhages, varying from microscopic extravasations limited to the perivascular sheaths to large gross hemorrhages, were constantly present in the midbrain and

pons. These hemorrhages were believed to be caused by prolonged prestasis due to pressure of the tumor, followed by complete stasis brought on rapidly or suddenly by any increase in pressure, due either to edema or to the engagement of the elongated temporal lobe beside the midbrain. The prognosis in the case of any tumor of the temporal lobe is serious when engagement of the temporal lobe has occurred. In cases of tumors in this region, more than of those in other situations, all manipulations not absolutely essential for diagnosis must be avoided. Lumbar puncture and ventriculography are dangerous in such cases.

LIBER, New York.

OLFACTORY MENINGITIS. MARCEL DAVID and HARDEN ASKENASY, Rev. neurol. **68**:489, 1937.

David and Askenasy report that olfactory meningiomas constituted 13 per cent of a series of 195 intracranial meningiomas and 21 per cent of basilar meningiomas. Next to meningiomas of the sphenoid ridge, they were the most frequent of the basilar group. They occurred chiefly in adults, of ages from 40 to 55. They may be classified topographically into three groups: anterior, middle and posterior. Tumors of the middle group are usually bilateral. Growing slowly in a silent area, such a tumor usually becomes very large and excavates deeply the two orbitofrontal lobes before manifesting itself clinically. It may infiltrate the base of the falx. It compresses, but does not adhere to, the optic nerves, from which it can easily be freed at operation. The anterior cerebral arteries, particularly their pericallosal branches, adhere to the tumor and supply it with large twigs. In one case the tumor grew into the nasal fossa. Tumors of the anterior group grow in the angle between the frontal bone, the cribriform plate and the falx. These tumors are usually unilateral and do not compress the optic nerves. Tumors of the posterior group are intermediate between the cribriform plate and the tuberculum sellae. They may be bilateral and compress both optic nerves or the chiasm, or they may be unilateral and compress only one optic nerve. There are rare tumors which spread over the entire floor of the anterior fossa.

Of thirteen cases studied, headache was the first complaint in seven cases, and anosmia, visual disturbance and mental disturbance in two cases each. Anosmia usually became complete, but often was not noticed by the patient. It was bilateral in twelve cases and unilateral in one. Papilledema was present in eight cases and was always bilateral. The syndrome described by Foster Kennedy was present in all cases, but was atypical in some, because of bilateral papilledema. The syndrome in its pure form is more frequent in association with meningioma of the sphenoid ridge. Mental disturbances were present at some stage of the disease in eleven cases. Dysmnesia, apathy, paradoxic euphoria, joviality and moria were the usual manifestations, simulating in one case those of dementia paralytica. Facial paresis of central type, unilateral trigeminal neuralgia, frontal ataxia and bilateral palsy of the abducens nerve were occasionally present. Roentgen signs included calcification in the tumor, basilar exostosis, erosion of the lesser wing of the sphenoid bone and excessive vascularization of the anterior portion of the calvarium. Stereoscopic ventriculography with the patient in the oblique position showed characteristic amputation of the frontal horns along a curved line which was concave anteriorly and lay astride the midline. Deformation of the third ventricle occurred only when the tumor was large and invaded the middle fossa. As a rule, the ventricles were narrow, as a result of cerebral edema. The operative approach was through a unilateral or a bilateral superior flap; if unilateral, this flap always extended beyond the midline. The anterior third of the frontal lobes was exposed by a dural incision extending to the sagittal sinus. The frontal lobes were usually edematous and often presented yellow discoloration. Removal of one frontal pole was necessary to expose the tumor. After the tumor was removed, strips of muscle or fascia were placed over the cribriform plates to prevent possible infection from the ethmoid cells or nasal fossae. The larger tumors required a two stage operation. The mortality rate was 66 per cent before, and 30 per cent after, the systematic use of electrocoagulation. Complete removal was not always possible.

LIBER, New York.

PATHOPHYSIOLOGIC BASIS OF MIGRAINE. VIGGO CHRISTIANSEN, Acta psychiat. et neurol. **12**:45, 1937.

On the basis of clinical observations, Christiansen concludes that the various types of symptoms in migraine imply vasomotor disturbances in two systems of intracranial blood vessels. The symptoms of focal cortical deficit and irritation—paresthesias, aphasia, scotomas and hemianopia—are the result of vasomotor disturbances in the blood vessels which lie on or within the brain, whereas the hemicrania, and probably the nausea and vomiting, are the result of vasomotor disturbance in the blood vessels supplying the dura mater.

YAKOVLEV, Waltham, Mass.

Peripheral and Cranial Nerves

DEFICIENCY SYNDROMES ASSOCIATED WITH CHRONIC ALCOHOLISM. JOHN ROMANO, Am. J. M. Sc. **194**:645 (Nov.) 1937.

Romano reports on a study of 131 patients with chronic addiction to alcohol. The age period from 30 to 50 included over 64 per cent of the total number of patients; 12.2 per cent were women. Of the 77 patients (58 per cent) who showed evidence of some form of neuritis, 61 (79 per cent) gave histories of inadequate diets. Eleven (68.7 per cent) of the women and 64 (55.6 per cent) of the men suffered from some degree of anemia. Every patient received a diet high in calories (from 4,000 to 5,000 daily) and in vitamins, plus substances containing vitamin B. Of patients with neuritis, 5 (6.4 per cent) failed to respond to vitamin therapy; 47 (61 per cent) showed partial, and 25 (32.4 per cent) complete, improvement. Romano concludes that vitamins B_1 and B_2 are of definite value in treatment of the deficiency syndromes associated with chronic alcoholism.

MICHAELS, Boston.

GLOSSOPHARYNGEAL NEURALGIA ASSOCIATED WITH ABSCESS OF THE PETROUS TIP FOLLOWING MASTOIDITIS. HENRY P. SCHUGT, Arch. Otolaryng. **26**:321 (Sept.) 1937.

The ninth, tenth and eleventh cranial nerves are adjacent to the petrous pyramid as they pass through the jugular foramen, and may become involved in petrositis. Disturbance of these nerves may produce the condition known as Vernet's syndrome, or the syndrome of the jugular foramen. It is marked by dysphagia, anesthesia or hyperesthesia of the soft palate and pharynx, loss of taste in the posterior part of the tongue (glossopharyngeal nerve), paralysis of the vocal cord on the affected side (vagus nerve) and disturbance in function of the sternocleidomastoid and trapezius muscles (spinal accessory nerve). The syndrome has been reported in association with metastatic tumor of the petrous tip, thrombosis of the transverse sinus and thrombosis of the bulb of the jugular vein; involvement of the glossopharyngeal nerve alone has been described in cases of thrombosis of the jugular bulb. The glossopharyngeal nerve lies closer to the petrous tip than the other two nerves and may become involved first in petrositis.

Schugt reports a case of petrositis associated with neuralgia of the glossopharyngeal nerve. In the literature no previous record of isolated neuralgia of the glossopharyngeal nerve associated with suppuration of the petrous tip was found. A case is reported in which simple mastoidectomy on the right side was followed by severe pain in the right eye and lower teeth, with continued drainage from the wound accompanied by pain in the right side of the throat. Pain in the eye and teeth was accentuated by swallowing. Examination of the pharynx, nasopharynx and larynx showed no pathologic involvement. There was hyperesthesia of the pharynx on the right side. The wound was explored; a fistula posterior to the lateral semicircular canal was enlarged, and the large abscess in the petrous tip was evacuated; this was followed immediately by relief from pain in the eye, teeth and throat.

HUNTER, Philadelphia.

THE REFLEXES IN THE PROGNOSIS OF TRANSVERSE LESIONS OF THE SPINAL CORD. ERIC OLDBERG, J. A. M. A. **110**:104 (Jan. 8) 1938.

It is now recognized that a reasonably rapidly produced total transverse lesion of the spinal cord in man will result clinically in (1) a stage of muscular flaccidity and complete loss of tendon and plantar reflexes, usually lasting from one to several weeks, (2) a stage of reflex activity, of variable duration, depending on the occurrence of any toxic febrile state and (3) a final stage of inanition. There are rare exceptions in which the first stage is permanent, particularly when the level of the lesion is caudal enough to approach the lumbar enlargement. There are also cases in which there is response from the outset to plantar stimulation, either flexor or extensor. In the main, however, these rules are axiomatic. The astute observer has come to rely greatly on the tonicity of the muscles and the state of the tendon reflexes of the lower extremities during the initial stages of any paraplegia in determining his predictions for the future. If mechanical trauma to the cord merely concusses it and produces transitory flaccidity and loss of reflex activity, continuance of the condition for any length of time almost invariably indicates permanent and complete disability. In the case of paraplegia caused by neoplasm and infection, the same prognosis applies to an even shorter-lived appearance of the manifestations of "spinal shock." Paraplegia from any source when associated with complete flaccidity and total absence of tendon reflexes existing more than a day or two, in the case of trauma, or more than a few hours, in the case of neoplasm and infection, is an almost hopeless prognostic sign, despite removal of the cause. In the treatment of acute conditions causing paraplegia, such as epidural abscess and malignant growths, immediate operation is advisable.

EDITOR'S ABSTRACT.

NEUROLOGIC COMPLICATIONS FOLLOWING ADMINISTRATION OF VACCINES AND SERUMS. L. J. ROBINSON, New England J. Med. **216**:831 (May 13) 1937.

Robinson discusses the occurrence of a case of flaccid paralysis of peripheral nerves following the prophylactic administration of typhoid-paratyphoid A and B vaccine. Its recognition led to consideration of similar neurologic complications which are occasionally encountered in the administration of serums, antitoxins and vaccines. Careful elimination was made of other possible causes of the paralysis in this case, which occurred four days after the second injection of the vaccine. At this time there was left foot drop, followed by atrophy and reaction of degeneration. Physical therapy was administered; three and a half months after the onset recovery was practically complete, and improvement was still progressing. Differential diagnosis demands distinction from peripheral paralyses caused by anterior poliomyelitis, lead poisoning, diabetes, alcoholism and avitaminosis. In commenting on possible etiologic mechanisms, Robinson considers the phenolic compound so frequently used as a preservative in serums and vaccines. In this connection there is presented the evidence which incriminates triorthocresyl phosphate as the cause of peripheral neurologic involvement in apiol and Jamaica ginger poisoning. The similarity in both the symptomatology and the pathologic manifestations in these cases, in cases of paralysis following administration of serums and vaccines and in a reported case of experimental phenol poisoning in a monkey is pointed out.

EDITOR'S ABSTRACT. [J. A. M. A.]

Vegetative and Endocrine Systems

ADRENAL CORTICAL ADENOMA WITH ABSENCE OF THE OPPOSITE ADRENAL. F. D. W. LUKENS, HARRISON F. FLIPPEN and F. M. THIGPEN, Am. J. M. Sc. **193**: 812 (June) 1937.

Lukens and his co-workers report a case of adenoma of the adrenal cortex in which the patient was operated on and died. Autopsy revealed absence of the opposite adrenal gland. The patient was a woman aged 25 with abdominal obesity,

general hirsutism, loss of hair on the scalp, amenorrhea and hypertension (210 systolic and 140 diastolic). Examination revealed generalized decalcification of the bones and diminished dextrose tolerance. Injection of air into the retroperitoneal space revealed a possible tumor on the right side. Laparotomy revealed a well encapsulated tumor, 3.5 by 3 by 3 cm. in diameter, in the right adrenal gland. Fever of from 102 to 104 F. persisted until death, eight days later. The prompt fall of blood pressure to a normal level after removal of the tumor was striking. The significant observations at autopsy were lipoid nephrosis, mild benign nephrosclerosis and osteomalacia. The left adrenal gland was absent. The rest of the right adrenal gland was grossly normal, but was much smaller than usual. The adrenal tumor was cellular, with cells of the cortical type. There was no tumor of the pituitary but the basophil cells showed the hyaline change of Crooke. The cause of death cannot be clearly stated. The case was one of an adrenal tumor associated with a fully developed Cushing syndrome. The authors state that before the removal of a tumor of the adrenal cortex the opposite side should be inspected to make sure that the other adrenal gland is present.

MICHAELS, Boston.

HYPERINSULINISM. EUGENE ZISKIND, WALTER BAYLEY and EDGAR F. MAUER, Arch. Int. Med. **60**:753 (Nov.) 1937.

The final report of a case of hyperinsulinism, including necropsy observations, is made. A youth aged 19 was first seen on admission to the hospital in coma, on Sept. 8, 1930. He was observed for four years, during most of which time he was in the hospital. Death occurred during a hypoglycemic episode, probably from asphyxia. Symptoms suggesting hypoglycemic reactions had been present for approximately eighteen months before admission to the hospital. Two abdominal explorations were performed, but no abnormality of the pancreas was detected.

Necropsy revealed an adenoma of the pancreatic islets. The brain was of average size for an adult; the dura was normal. There were moderate pial injection and milky thickening of the leptomeninges over the entire anterior portion of the hemispheres. The cerebellar tonsils showed a slight degree of herniation, and the uncinate gyri, minor grooving; the cerebral convolutions, however, were not flattened. The blood vessels at the base of the brain were soft and thin walled. Coronal section revealed symmetric ventricles, which were not dilated. The brain stem and cerebellum were unchanged. Other than the modifications incident to asphyxiation, nothing of significance was seen on gross examination.

The characteristics of the hypoglycemic attacks were numerous and varied. Frequently the initial symptoms were hunger, weakness, anxiety, twitching of the right hand or right side of the face and numbness of the right hand. In mild attacks nausea, vomiting, headache, drowsiness, trembling, perspiration, facetiousness, pugnacity, ataxia and loss of speech might occur. More severe symptoms were aphasia, hemiparesis, confusion, involuntary laughing, crying and singing, delusions, hallucinations, convulsions and coma. Occasionally the patient had a convulsive seizure without premonitory symptoms other than those of hypoglycemia. Objectively, there were pallor, coldness of the extremities, tremor, profuse perspiration, dilatation of the pupils, subnormal temperature and increase in the pulse pressure. Tachycardia was so frequent that it could not be utilized as an indication of impending hypoglycemia. Occasionally a low value for the blood sugar was recorded without any subjective or objective disturbance. Always, however, hypoglycemia was found in the presence of symptoms.

The convulsive attacks varied considerably in their totality. Twitching of the right hand or right eyelid, jacksonian seizures on the right and generalized convulsions, with or without residual hemiparesis and the Babinski sign, occurred as isolated manifestations. Almost always the patient regained consciousness rapidly after a convulsion, at which time the level of the blood sugar had returned to normal. The earliest effect on the psychomotor reactions was decrease in the auditory memory span for sentences. Impairment of mathematical ability and disorientation occurred at later lower hypoglycemic levels. The psychologic functions manifested impairment at higher glycemic levels than did the motor. Speed

and endurance diminished with increasing hypoglycemia. The spinal fluid pressure was elevated both when the value for the blood sugar was low and during a hypoglycemic attack. A definite latent period existed between the time of change in the value for blood sugar and restoration of equilibrium in the blood sugar-spinal fluid sugar ratio. At one time during the latent period, the sugar content of the spinal fluid was at a higher level than that of the blood. The effect of mental work on the level of the blood sugar was tested, but the results were inconclusive.

BECK, Buffalo.

THE EFFECT OF COMPLETE AND PARTIAL HYPOPHYSECTOMY IN ADULT ALBINO RATS ON WATER, CHLORIDE, SODIUM, POTASSIUM AND SULFUR METABOLISM. M. SANDBERG, D. PERLA and O. M. HOLLY, Endocrinology **21**:346 (May) 1937.

Sandberg and his co-workers studied the effect of hypophysectomy on water, chloride, sodium, potassium and sulfur metabolism in eleven male and ten female albino rats. In the male rats pronounced polydypsia and polyuria occurred after hypophysectomy. This was still present ten weeks after operation. In the female rats the intake and output of water returned to normal after five weeks. In the partially hypophysectomized animals the rise was much less pronounced and persisted for only three weeks. Urinary excretion of chlorides in the male rats rose from 43 per cent of the intake during the period of control to 86 per cent during the first three weeks after hypophysectomy, and fell to 68 per cent ten weeks after operation. In the females the increase, from 51 to 68 per cent of the intake, lasted for only three weeks. It dropped to normal during the next two weeks, and even to below normal (33 per cent) during from the sixth to the tenth week after operation. In the partially hypophysectomized males there was little change in the urinary excretion. Retention in the male rats dropped considerably. This was not due to simple washing out of the chlorides as a result of the pronounced diuresis, since the absolute amounts excreted by the kidneys showed little variation, regardless of the fact that the intake decreased by half. Fecal excretion of chlorides dropped with the diminished intake in all animals. The urinary excretion of sodium and potassium followed closely that of the chloride ion. The authors state that this inability to retain sufficient potassium agrees with the finding by Marenzi of a decrease in the potassium content of the blood plasma of hypophysectomized dogs. In the male rats total urinary excretion of sulfur rose from 17 per cent of the intake during the period of control to 48 per cent during the first five weeks after hypophysectomy, and fell to 36 per cent ten weeks after operation. The excretion of inorganic sulfates returned to normal after three weeks. The disturbance in sulfur metabolism encountered in hypophysectomized rats is probably attributable to the lack of adrenotropic hormone, which prevents the proper functioning of the adrenals. Excretion of neutral sulfur increased. The percentage of fecal sulfur excreted was unchanged, though absolute values fell with the diminished intake. In the female rats the excretion of total urinary sulfur and of inorganic sulfates dropped to normal three weeks after operation, and then to below normal. Excretion of neutral sulfur was increased; that of fecal sulfur remained unchanged. This indicates a disturbance in the endogenous sulfur metabolism of the same type as that in adrenalectomized animals, suggesting that the hypophysis controls sulfur metabolism by way of the adrenals. In the partially hypophysectomized rats there was little or no change in sulfur metabolism.

PALMER, Philadelphia.

OBSERVATIONS ON CARBOHYDRATE METABOLISM FOLLOWING IRRADIATION OF THE PITUITARY GLAND. M. PIJOAN and R. ZOLLINGER, Endocrinology **21**:357 (May) 1937.

Pijoan and Zollinger studied ten women in apparently good health except for menopausal symptoms, who were subjected to roentgen radiation of from 1,400 to 1,600 skin doses over the pituitary gland for four days. Studies were carried

out before and after irradiation. The ages varied from 29 to 50, the average being 42. The authors report that in 35 per cent of cases there was a definite sustained decrease in the number of hot flashes and that no ill effects except an occasional headache were noted in any of the cases after treatment. They found no change in carbohydrate metabolism after irradiation of the pituitary gland, with the dosage used. Massive irradiation over the pituitary body cannot be directed entirely to the gland itself and must act as well on nerve centers near this gland.

PALMER, Philadelphia.

PUBERTAS PRAECOX (MACROGENITOSOMIA). H. P. RUSH, J. B. BILDERBACK, D. SLOCUM and A. ROGERS, Endocrinology **21**:404 (May) 1937.

Rush and his colleagues report three cases of hypergenitalism (macrogenitosomia) in one family. The cases were those of a father, aged 33, and his two sons, aged 5 and 8 years. The sons showed signs of typical hypergenitalism. The father, at the time of writing, had signs of a hypogonadal syndrome. Androgen was demonstrated in the urine of all three patients by means of the capon comb test. Normally, this substance is not found in the urine of boys under 10 years of age. The gonadotropic principle could not be demonstrated in any of the cases. No associated signs or symptoms indicated tumor or marked hypertrophy of the pineal gland, adrenal cortex, gonads, pituitary or thymus. There were no signs or symptoms of a cerebral lesion. The condition in these cases seems to fall in the group called primary, primary-constitutional or congenital pubertas praecox. In addition to the three cases reported, the family history disclosed five other instances of pubertas praecox in four generations. The condition seems, therefore, to have been determined genetically. It is possible that an abnormal responsiveness to gonadotropic hormones may be inherited in these cases.

PALMER, Philadelphia.

PITUITARY DWARFISM WITH DIABETES MELLITUS. H. G. BECK and G. M. SUTER, Endocrinology **22**:115 (Jan.) 1938.

Beck and Suter report the results of treatment in the case of a boy with pituitary dwarfism associated with diabetes mellitus. At the age of 15, when treatment was instituted, he was 47 inches (119 cm.) in height and weighed 59½ pounds (27 Kg.). During the first ten months he received hypodermically 1 cc. of gonadotropic substance from the urine of pregnant women (antuitrin-S) every other day and 10 grains (0.65 Gm.) of an extract of the anterior lobe of the pituitary daily by mouth. At the end of this treatment and for the ensuing twenty-one months, a pituitary extract containing the growth hormone (antuitrin-G), in doses of 1 cc. every other day, was substituted. There was an increase in height of 8.37 inches (27.8 cm.) during the two and a half years. Development of the external genitalia, from infantile size to full maturity, and of the secondary sexual characteristics was striking. No effect on the diabetes following the pituitary therapy was observed.

PALMER, Philadelphia.

Treatment, Neurosurgery

THE TREATMENT OF SYPHILIS WITH ARTIFICIAL FEVER. CLARENCE A. NEYMANN, Am. J. Syph., Gonor. & Ven. Dis. **22**:92 (Jan.) 1938.

Review of the literature concerning artificial fever in the treatment of neurosyphilis revealed that 975 patients had been studied by other authors. Of this number, 27 per cent had a complete remission, while 354 (36 per cent) were reported as showing improvement and were said to be no longer in need of hospitalization. Twenty-two, or approximately 2 per cent, died as a direct result of treatment. The statistics for malarial therapy showed that about 43 per cent achieved a remission or were greatly improved. Electropyrexia has, therefore, increased the total rate of improvement by 21 per cent. The death rate attributed

to malarial therapy varied from 10 to 30 per cent. Neymann states that when electromagnetic induction, combined with an air-conditioned treatment cabinet for maintaining fever, was used by an experienced personnel, there were no deaths. An effective adjunct to artificial fever therapy was the administration of pentavalent arsenic at the height of the fever. The communications of other observers prove that tabes is improved by electropyrexia. Of 114 patients reported, 75 (66 per cent) were said to show improvement, and 39 (34 per cent), no signs of amelioration. Neymann treated 8 patients with early stages of tabes. The disappearance of pain and improvement in general health were outstanding. In each patient the crises ended after the sixth or eighth treatment with electropyrexia. Although no modification of abnormal pupillary or reflex responses has ever been noted, the ataxia improved remarkably. Twenty biweekly treatments with artificial fever should be given, in which the temperature should be above 39.7 C. (103.5 F.) for eight hours and above 41 C. (105.8 F.) for at least two of the eight hours. Bismarsen should be injected in 0.2 Gm. doses during each fever treatment. Tryparsamide is not recommended because it has been found to be dangerous during hyperthermia.

The use of electropyrexia in the early stages of human syphilis, although still experimental, can arrest the progress of the disease, particularly when combined with arsphenamine and the heavy metals. Patients who under treatment are not relieved from clinical or serologic symptoms are frequently benefited if large doses of neoarsphenamine are administered during the height of the fever. In most cases this treatment seems to arrest syphilis promptly in the early stages.

BECK, Buffalo.

SURGICAL REPAIR OF THE FACIAL NERVE. STERLING BUNNELL, Arch. Otolaryng. **25**:235 (March) 1937.

Various intracranial conditions and certain general infections and toxemias cause paralysis of the facial nerve. In not over 7 per cent of cases is palsy of the facial nerve due to purulent otitis media. Paralysis following fracture of the skull or gunshot wound usually recovers spontaneously. The nerve may be injured outside the stylomastoid foramen by tumor, abscess, inflammation of the jaw or wound. In most cases paralysis of the facial nerve is due to trauma during mastoidectomy, toxemia or exposure to cold. The site of injury in mastoidectomy is usually in the vertical portion of the bone, just below the bend. In Bell's palsy the lesion is due to swelling of the nerve, usually in the most distal part of the canal, as shown by the fact that taste is retained. Immediate decompression should result in cure, but since 80 per cent of the patients recover spontaneously it has been the rule to advise surgical intervention if recovery does not take place in six months. In some cases it has resulted in recovery even at a later date. Duel advises operation in cases in which there is no faradic response. Persistence of faradic response and a quick response to the galvanic current indicate a mild lesion that will heal. If signs of complete severance of the nerve are present, with reaction of degeneration and rapid and complete atrophy, there is no method of distinguishing between physiologic and organic block except by observation. Repair by anastomosis is now obsolete. The present methods of repair of the facial nerve consist of decompression, suture or free nerve graft; if the nerve is irreparably damaged or the facial muscles have undergone degeneration, plastic reconstruction is advisable. Bunnell states that he was the first person successfully to suture the facial nerve within the temporal bone. He reports eight cases of surgical repair of the facial nerve.

HUNTER, Philadelphia.

STREPTOCOCCIC OTITIC MENINGITIS WITH RECOVERY. HENRY DINTENFASS, Arch. Otolaryng. **25**:311 (March) 1937.

Dintenfass reports a case of recovery from streptococcic meningitis. A child aged 8 years had acute otitis media, which necessitated paracentesis on the second day. Nine days after onset of the disease simple mastoidectomy was performed

and pus was found in the neighborhood of the antrum. The dura over the middle fossa was exposed, but no changes were seen. Symptoms of meningitis developed twenty-five days after the operation. The spinal fluid was cloudy and contained 9,800 cells; a culture of the spinal fluid was positive for Streptococcus haemolyticus. Findings in the urine suggested acute glomerular nephritis. Operation was again performed, and the bone was removed over the middle and posterior fossae. The bone showed no evidence of pathologic change. On the following day the dura over the middle fossa was incised. There was no unusual tension. The cerebrospinal fluid escaped freely. Subsequent cultures of the fluid were sterile. An intraspinal injection of polyvalent antistreptococcic serum was given and was repeated every twelve hours for five days. On the twenty-eighth day of the disease paralysis of the left external rectus muscle appeared. A severe serum reaction developed, after which the condition progressed to full recovery six weeks after operation; the spinal fluid was then clear and free from organisms, and there was recovery from paralysis of the external rectus muscle. Since the spinal fluid was sterile after dural incision and drainage, and before the introduction of serum, recovery cannot be attributed to the serum treatment.

HUNTER, Philadelphia.

MENINGITIS DUE TO THE TYPE III PNEUMOCOCCUS: REVIEW OF THE LITERATURE AND REPORT OF A CASE OF OTITIC ORIGIN WITH RECOVERY FOLLOWING RADICAL MASTOIDECTOMY AND LABYRINTHECTOMY. CHARLES H. ALLMAN, Arch. Otolaryng. **25**:653 (June) 1937.

Allman found in the literature four cases of recovery from meningitis due to the type III pneumococcus. These patients were given antipneumococcus serum intraspinally, intracisternally and intramuscularly; they received also a solution of ethylhydrocupreine hydrochloride intraspinally and retention enemas of potassium permanganate. Allman reports a fifth case in which the disease followed chronic purulent otitis media. The patient had headache, vomiting and pain in the back. She was semiconscious and showed the usual signs of meningitis. The spinal fluid contained 9,000 cells, 88 per cent of which were polymorphonuclear leukocytes. Culture of the cerebrospinal fluid showed type III pneumococci. Radical mastoidectomy and labyrinthectomy were performed on the left side. The patient remained unconscious for forty-eight hours after operation. After this the spinal fluid count began to improve. On the fifth day after operation culture of the spinal fluid showed no growth. The patient was discharged forty days after admission. The operation was performed six years ago; she has remained well since, but the ear has continued to discharge. Of the five patients who have recovered, four were treated by subarachnoid drainage, lumbar or cisternal puncture or both. Two received antipneumococcus serum only; one, antipneumococcus serum and ethylhydrocupreine hydrochloride, and one, no subarachnoid therapy. In most cases the meningitis originated from the middle ear or the mastoid. The organisms were probably of low virulence, but surgical intervention seemed to be an important factor. Allman considers the following points important in treatment for pneumococcic meningitis: (1) early diagnosis and identification of the organism; (2) elimination of the focus by surgical means; (3) early administration of highly concentrated serum, and (4) measures to make sure that the therapeutic agent reaches all areas of the subarachnoid space.

HUNTER, Philadelphia.

MENINGITIS DUE TO THE TYPE IV PNEUMOCOCCUS, WITH RECOVERY. PAUL S. MERTINS and PAUL S. MERTINS JR., Arch. Otolaryng. **25**:657 (June) 1937.

Recovery from meningitis due to the type IV pneumococcus is extremely rare. Tripoli found 1 instance of recovery in 110 cases in ten years at the New Orleans Charity Hospital. Reports of 30 other cases of recovery were found in the literature. Mertins and Mertins report the case of a girl aged 13 with

meningitis following bilateral purulent otitis media. The patient was admitted to the hospital in an almost moribund state. Lumbar puncture showed a cloudy spinal fluid, containing 2,000 cells. There were occasional gram-positive diplococci on smears and a pure culture of pneumococci. The Neufeld reaction was negative for types I, II, III, V, VII and VIII, and agglutination tests for types I, II and III confirmed this result. The culture was avirulent for white mice three days later. A culture of the blood was sterile. The authors administered 10 cc. of the disodium salt of 4′-sulfamidophenyl-2′-azo-7′acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid every six hours. Extensive, simple mastoidectomy was performed. Since an untyped pneumococcus was reported, the authors administered 5 grains (0.3 Gm.) of sulfanilamide every four hours. A small blood transfusion and a small intravenous injection of solution of formaldehyde were given. On the sixth postoperative day the patient became worse and passed into deep coma; the pulse was barely palpable, and the temperature was 105.8. All medication was discontinued, and the prognosis of an immediate fatal outcome was made. Three hours later the child suddenly woke, asked for a pickle and said that her head felt fine. The temperature dropped by crisis and remained normal.

HUNTER, Philadelphia.

PHYSICAL THERAPY IN INFANTILE PARALYSIS. FRANK R. OBER, J. A. M. A. **110**:45 (Jan. 1) 1938.

Ober discusses the early orthopedic, nursing and physical measures which are necessary in preventing crippling from infantile paralysis and in restoring as much function as possible in each case. It is during the acute stage that all the resources of the attending physician, nurse and orthopedic surgeon are often needed. Treatment during the febrile portion of the acute stage is mainly that of medical and nursing care, but the attending physician should not consider that convalescence has begun as soon as the fever has subsided. It is during this time that the patient is apt to have exquisite tenderness in the legs, calves, thighs, hips and back and in the adductor region of the shoulders. The tenderness is not always confined to the paralyzed members. Patients who are sensitive in these parts may assume protective positions of flexion in order to relieve pain, and thereby deformities may develop. To prevent the occurrence of such conditions, properly covered and padded wire splints must be applied to hold the extremities in the position of comfort. As the soreness disappears, flexed limbs will gradually straighten, and the splints may be adjusted accordingly. The splints are useful in relieving pain and preventing deformities. No massage or exercises should be started during the stage of tenderness, since they do nothing but increase the pain and delay favorable progress. Absolute rest in bed and daily hot packs or hot baths, at a temperature of 105 F., must be insisted on, since these are more effective than any other form of therapy. The patient will often move his extremities a little in the hot bath without detriment. As soon as all the signs of tenderness have disappeared (second stage), rehabilitation should be begun by an expert physical therapy technician who has complete knowledge of muscular function. Deformities must be prevented if possible by proper attitudes of the patient and careful splinting of the extremities and back, if necessary. The physical therapy technician should make a complete examination of the muscles in order to evaluate the loss of power in each muscle or group of muscles, as the case may be. If the muscles are too weak to function against gravity and friction, these obstacles should be removed. Exercises given in a pool or tank of warm water eliminate friction. The strong muscles must not be treated at the expense of those that are weak. As soon as a muscle shows the first sign of flagging, it should be rested. During the early part of the convalescent stage, complete rest must be insisted on. The duration of the physical treatment should be indefinite; i. e., it must be continued as long as recovery can be demonstrated. Early walking should be discouraged. The third stage is usually the period following the maximal recovery of power of muscles and has been arbitrarily placed at two years. It is not

uncommon for muscular power to increase for many years after this. It is during this stage that fixed deformities must be relieved by operative measures, such as arthrodeses and tendon transplantations. During the period of immobilization after each procedure, a physical therapy technician should teach the patient how to exercise the limbs to improve function and how to exercise the transplanted muscle so that it will take on the function of the muscle for which it is substituted.

QUININE IN MYOTONIA AND PROSTIGMINE IN MYASTHENIA: CLINICAL EVALUATION. FOSTER KENNEDY and ALEXANDER WOLF, J. A. M. A. **110**:198 (Jan. 15) 1938.

It is one year since the appearance of Wolf's report that quinine abolished the myotonus of congenital and atrophic myotonia and two years since Walker discussed the use of prostigmin (the dimethylcarbamic ester of 3-hydroxylphenyltrimethylammonium methylsulfate) in alleviating the muscular weakness of myasthenia gravis. In this period Kennedy and Wolf have studied, seen or been in indirect contact with nine patients with myasthenia gravis, nine patients with myotonia congenita and eighteen patients with myotonia atrophica. Every patient with myasthenia gravis showed an immediate excellent response to prostigmin, with generalized increase in muscular power. Patients previously bedridden and gasping for breath became ambulatory and took light exercise. However, within from one to four months four patients began to show a progressively poorer response to prostigmin, so that the dose had to be increased gradually to maintain swallowing and to aid respiration. In spite of increased medication, these patients were at times almost at the point of death. Sweating was marked in all cases. It seemed that if prostagmin was given beyond a certain point patients became refractory toward its beneficial effects. Accordingly, the administration of prostigmin was discontinued for from thirty-six to forty-eight hours, during which time the administration of potassium chloride and ephedrine sulfate was pushed to a point just below intolerance. Swallowing became impossible, so that feeding by tube was required. After from thirty-six to forty-eight hours prostigmin medication was resumed, in 1 case with one ampule (0.5 mg.) twice a day. This patient showed a much better response to two ampules after a two day abstinence than she previously had to twenty-four ampules. Gradually, however, the amount has had to be increased to twelve ampules a day, and again she is much less responsive. A second patient has maintained a fair degree of strength while receiving four ampules a day after a two day abstinence. A third patient was formerly given from eighteen to twenty-four ampules, despite which swallowing remained impossible. He now has had no prostigmin for four months and shows few signs of deprivation. He may be in a state of spontaneous remission. The dose in the fourth case has not yet been reduced. Why certain of the patients should after a while become refractory to prostigmin is not clear, nor can Kennedy and Wolf be certain that the patients who have so far responded well will not at some time become refractory. The refractory character of prostigmin medication after an early extended period of usefulness has been noted by other investigators. The eighteen patients with myotonia atrophica and the nine with myotonia congenita have been treated with quinine during the past year. Quinine abolishes myotonus for as long as it is administered. In two patients there was some diminution of myotonus after the use of quinine was discontinued. Oral administration of from 2½ to 5, 10 or 15 grains (0.16 to 0.32, 0.65 or 0.98 Gm.) of quinine hydrochloride two or three times a day has consistently eliminated myotonus.

EDITOR'S ABSTRACT.

FURTHER EXPERIENCES IN THE INSULIN-HYPOGLYCEMIA TREATMENT OF SCHIZOPHRENIA. D. EWEN CAMERON, J. Nerv. & Ment. Dis. **87**:14 (Jan.) 1938.

Cameron reports observations in the treatment of twenty schizophrenic patients with doses of insulin running as high as 200 units a day for weeks or months. In fifteen patients the disease had persisted more than a year. He noticed that during the course of each hypoglycemic reaction there was an optimal stage at

which sugar should be administered to terminate the reaction and, further, that the psychologic state present at the moment hypoglycemia was interrupted tended to persist thereafter or to be followed by more or less predictable behavior patterns. Cameron believes that this is one of the major guiding principles of the insulin treatment. There are four favorable periods for interruption of the insulin reaction: The first is the period of wakefulness, accessibility and clarity; the second, the phase of convulsive movements, which may cease, to return just before the next period; the third, the stage of incipient coma, and the fourth, the stage of deep coma, with no response to stimulation and absence of the corneal reflex. It seems expedient to terminate the reaction in the first or the fourth stage. Cameron was unable wholly to confirm Sakel's concept of "reversal of the psychosis," by which is meant the tendency of periods of lucidity to appear at first only during the hypoglycemic state and later only between insulin reactions, with psychotic symptoms during the hypoglycemia. The work tends to show that by careful interruption of the insulin reaction during periods of lucidity, considerable improvement may be achieved. Patients whose condition improves with treatment tend to show an increase in weight of from 3 to 7 pounds (1.3 to 3.2 Kg.) a week. Heterosexual interest and activity also increase during improvement, together with increasing sociability, lessened tendency to projection and "normalizing" of the formal behavior. Relapses are frequent during apparently favorable management, and may be abrupt and traceable to unsuccessful treatment or to unwise probing into the patient's difficulties or may be insidious with gradual loss of weight and interest. Cameron emphasizes that in his hands the method has not yet yielded the high remission rates reported from European centers. Of twenty subjects, four were able to return home on a fairly stable basis. Three others, though still under treatment, were able to go home on visits. In seven cases treatment had been stopped because of poor physical condition or an unfavorable response, while in six treatment was still in progress. If improvement occurs, it manifests itself within a few days, or at most in two or three weeks after the commencement of therapy.

MACKAY, Chicago.

TREATMENT OF SCHIZOPHRENIA WITH INSULIN. M. MÜLLER, Ann. med.-psychol. **94**:649 (Nov.) 1936.

Müller found that the dose of insulin required to produce shock varied with each patient. Usually a dose of from 40 to 100 units was necessary during the first phase. However, in some cases 10, or even 8, units produced a shock, while in others 200, or even 260, units had no effect. Knowledge of each patient's resistance is of paramount importance. Resistance may vary in the same patient during treatment. It may increase, requiring higher doses to produce shock, or more frequently sensitization to insulin may develop. One patient, for example, did not react until a dose of 190 units was reached, and thereafter had severe shock after only 80 or 90 units. There is no relationship between the severity of the clinical symptoms and the hypoglycemia. Some patients showed no symptoms with a blood sugar as low as 30, or even 25, mg. Others lapsed into profound coma with the level of the blood sugar at 70 mg. The blood sugar content cannot, therefore, be relied on as a criterion of safety in carrying out the treatment.

Complications are epileptic convulsions, excessive myoclonic contractions, syncope, respiration of the Cheyne-Stokes types, arrest of respiration and spasm of the glottis. Even after recovery from shock, complications may arise. Sometimes, several hours after an induced shock or during the night a spontaneous or a "delayed" shock may develop. In Swiss clinics, including Müller's, a total of 136 patients were treated, with 1 death. The fatality occurred in the case of a woman aged 51, from acute pulmonary edema two hours after the neutralizing injection of dextrose. The patient had previously withstood several insulin shocks without complications. The total incidence of deaths in the clinics of Switzerland and Vienna thus far is 1.3 per cent. The therapeutic results depend on the duration of illness. Of the patients with disease of less than six months' duration,

73 per cent recovered completely, the remission of symptoms having persisted for one year, and 16.8 per cent were improved. Of the group who had been ill for from six to eighteen months, 50 per cent recovered and 32 per cent were improved, whereas of those who had been ill for more than eighteen months only 0.5 per cent recovered and 44.5 per cent were improved. Of 136 patients treated 60 had complete remission of symptoms. The paranoid form of schizophrenia, the worst from the standpoint of prognosis, seemed to be the most responsive to treatment.

YAKOVLEV, Waltham, Mass.

"BULGARIAN TREATMENT" IN CARE OF CHRONIC POSTENCEPHALITIC PARKINSONISM, FROM THE CLINICAL, STATISTICAL AND INSTITUTIONAL POINTS OF VIEW. LEVI BIANCHINI, Arch. gen. di neurol., psichiat. e psicoanal. **18**:35, 1937.

The "bulgarian treatment" consists in the administration of a fresh decoction of the roots of plants of the Atropa belladona family obtained in Bulgaria. Five per cent by weight of the powdered roots is boiled in white wine, and the loss by evaporation is made up by adding fresh amounts of wine. The dose begins with 6 cc. daily and is raised rapidly, usually to 60 cc. and occasionally higher. The treatment must be individualized. Breaks in treatment are often advisable, and the dosage should be reduced in warm weather.

So successful has this treatment been in Italy—over 2,000 patients have been treated—that special clinics for its practice have been established in various medical clinics. More rapid and complete relief from tremor and rigidity and improvement in the psychologic state are obtained by this method than by treatment with the atropine group in other forms, and with less danger of toxic results. The treatment should be combined with a predominantly vegetarian diet, exercises and psychotherapy, usually best administered in special institutions.

PUTNAM, Boston.

EXPERIENCES WITH INSULIN SHOCK TREATMENT FOR SCHIZOPHRENIA. ZOLTÁN VON PAP, Monatschr. f. Psychiat. u. Neurol. **94**:318 (Jan.) 1937.

Insulin shock therapy has been used by von Pap in fifty-seven cases of schizophrenia. At first insulin was given in doses of from 20 to 30 units every half-hour until unconsciousness occurred, but because of the difficulty in producing hypoglycemic shock with this method the following procedure was adopted: A single injection of insulin was given daily, beginning with 40 units, and the dose was increased 20 units on each succeeding day. The first dose that led to hypoglycemic shock was used throughout the course of treatment. Sometimes it could be decreased later, however, since repeated hypoglycemic shocks often increased the sensitivity of the patient to insulin. If the pulse was of good quality and the respirations were quiet, the patient was allowed to remain in an unconscious state for from one to two hours. The coma was then terminated by slowly injecting from 40 to 80 cc. of a 40 per cent solution of dextrose intravenously. Hypoglycemic shocks were produced at intervals of two or three days until from twenty to thirty treatments had been given. Continuation of the treatment served no useful purpose. In some cases favorable results were obtained with ten hypoglycemic shocks. It was necessary to watch the patient for a considerable period after consciousness had been regained, for loss of consciousness occasionally occurred hours later. Conditions such as epileptic seizures, noisy and labored breathing, cyanosis of the face, marked slowing or acceleration of the pulse rate or a sudden drop in blood pressure were regarded as indications of danger that demanded immediate administration of sugar.

There was no constant relation between the amount of insulin given, the level of the blood sugar and the occurrence of unconsciousness. In some cases 60 units of insulin was sufficient to produce hypoglycemic shock, whereas in others doses of from 300 to 360 units were ineffective. The sugar content of the blood was

often lower in the precomatose period than during coma. The lowest figure obtained for sugar was 32 mg., but in some instances a value of 67 mg. was associated with prolonged periods of unconsciousness. In many patients loss of consciousness was preceded and followed by states of peculiar psychomotor unrest, in which active psychotic manifestations were observed. With continued improvement the so-called activation of the psychosis appeared less frequently, with fewer symptoms, and finally failed to occur. During hypoglycemic shock the patients often showed convulsive phenomena, many of which pointed to disturbances in function of the subcortical ganglia. After the return of consciousness aphasic symptoms of short duration were not uncommon, and transient paralyses of the ocular muscles, face or limbs were occasionally noted. Analysis of the effects of hypoglycemic shock on perception disclosed in all fields peculiar distortions which resembled those produced by hashish and mescaline. No deaths were directly attributable to the action of insulin, but two patients had high fever, with tetanic convulsions, athetoid and choreic movements and cardiac and respiratory disturbances, which lasted for several days. Occasionally vomiting occurred during coma, and in one case this led to aspiration pneumonia.

Of the fifty-seven patients treated by von Pap, twenty-two, or 38.59 per cent, showed improvement. Only the patients who were completely restored to their previous occupational and social levels were regarded as improved. In approximately 25 per cent of the group the psychosis was of more than two years' duration. Better results were obtained when the treatment was given earlier in the course of the illness. In fact, von Pap believes that this type of therapy should not be undertaken in cases in which the psychosis has lasted for more than one year. The therapeutic effects of the treatment are not based on any direct chemical or physiologic action of the insulin itself, for large amounts of insulin were ineffective when unconsciousness failed to occur. The favorable results must be attributed to the loss of consciousness, which loosens the deeper connections of the pathologic mental phenomena with the personality. This provides an opportunity for the critical faculties of the patients to be directed into normal channels, thereby allowing reestablishment of normal forms of behavior. As a result of his observations, von Pap has come to the conclusion that insulin shock therapy can be expected to produce satisfactory results when used with care in properly selected cases of schizophrenia.

ROTHSCHILD, Foxborough, Mass.

Cerebellum and Brain Stem

LOCALIZATION WITHIN THE CEREBELLUM OF REACTIONS TO FARADIC CEREBELLAR STIMULATION. W. K. HARE, H. W. MAGOUN and S. W. RANSON, J. Comp. Neurol. **67**:145 (June) 1937.

Electrical stimulation of the cerebellum was applied by means of the stereotaxic instrument for information relating to functional localization in the normal monkey and the normal and decerebrate cat. Reactions were most frequently elicited from the medial cerebellar nuclei, the white substance which surrounds them and their efferent tracts. The cerebellum thus stimulated produced inhibition or contraction of skeletal muscles, whether flexor or extensor. No support was advanced for the belief that specific muscle groups have either an exclusive or a preponderant representation within any lobule of the cerebellar vermis.

ADDISON, Philadelphia.

CEREBELLAR ABSCESS, WITH DIFFUSED SUPPURATIVE LABYRINTHITIS. A. S. FERNANDO and G. DE OCAMPO, J. Philippine Islands M. A. **17**:13 (Jan.) 1937.

Fernando and de Ocampo report a case of otogenic cerebellar abscess with recovery. The patient was admitted with symptoms pointing to labyrinthine disturbance. Hearing and caloric tests showed that the labyrinth was completely

irresponsive; there were phenomena, however, which could not be explained by this condition alone. The direction of the nystagmus, which was toward the side of the diseased ear and which was not to be expected in the case of a destroyed labyrinth, the continuous headache and insomnia and the mode of falling made the authors suspect the presence of intracranial involvement in addition to the diffuse suppurative labyrinthitis. This belief was strengthened by the presence of slight rigidity of the neck on the day before operation. This prompted lumbar puncture, which showed serous meningitis. The meningitis was of the irritative or protective variety. Suspicions were narrowed to a localized intracranial suppurative process —more specially, an abscess of the temporal lobe or the cerebellum. Symptoms and signs of involvement of the left temporal lobe were lacking. The presence of cerebellar abscess was then evident, and on the morning of the operation (Newman-Jansen endocranial technic) additional, though vague, localizing symptoms appeared in the form of weakness of the grip of the left hand and adiadokokinesia. When labyrinthitis and cerebellar abscess occur together symptoms are confusing. The patient was kept in the hospital for almost four months. Maximal drainage and minimal traumatism were assured by cautious insertion of a rubber drain. The pus obtained from the abscess was sterile, probably owing to disintegration of the bacteria by an unfavorable tissue reaction. The route of infection must have been through the labyrinth. Lumbar puncture made three months after operation revealed normal spinal fluid, which showed that the patient had recovered completely from the meningitis.

EDITOR'S ABSTRACT.

TUMOURS INVOLVING THE VENTRAL ASPECT OF THE PONS AND MEDULLA, INCLUDING TWO CHORDOMAS. L. D. STEVENSON and E. D. FRIEDMAN, Brain **59**:291, 1936.

Stevenson and Friedman report two cases of meningioma and two of chordoma involving the base of the brain. There is no symptom complex characteristic of tumors of the base of the brain. The authors believe that signs of involvement of one or both hypoglossal nerves or of other of the lower cranial nerves may indicate localization of the tumor in front of the pons and medulla rather than in the fourth ventricle. Many tumors at the base are latent and without symptoms, but they may involve any of the lower cranial nerves, from the eighth to the twelfth. They are frequently accompanied by disturbances in respiration and heart rate and by intermittent glycosuria. The more characteristic signs and symptoms include occipital headache, peculiar attitudes of the head, cerebellar ataxia and an intermittent course. "Hypoglossal fits" are exceedingly suggestive. Careful encephalographic studies may disclose encroachment on the cisterna pontis. In the main, one must be content with the diagnosis of a lesion of the posterior fossa.

A tumor of the fourth ventricle usually gives rise to Bruns' sign and signs of internal hydrocephalus, perhaps with evidence of distant pressure on the chiasm, due to herniation of the floor of the third ventricle. Cases of tumor of this region as a rule are characterized by absence of phenomena of involvement of the cranial nerves. Ependymoma of the fourth ventricle is apt to give rise to pain on turning the head, owing to extension of the growth either upward from the spinal cord or downward from the fourth ventricle.

An infiltrating tumor of the pons does not as a rule give rise to obstruction of the aqueduct of Sylvius; hence, there usually is no papilledema. Headache is frequently absent. Involvement of the pyramidal tracts is prominent in cases of glioma of the pons. In the authors' cases headache was an early and severe symptom, and pyramidal tract signs were practically absent in two cases. Involvement of the sensory division of the fifth nerve is likely to be present in association with infiltrating tumor of the brain stem, owing to implication of the ascending spinal root. Nystagmus is also especially frequent in cases of intrapontile lesions. Pain in the neck is rare in association with intrapontile glioma but is pronounced with extrapontile tumors; it occurs especially on movement of the head.

Vascular lesions of the pons and medulla are apt to give rise to more clearly defined syndromes, involving the distribution of the superior cerebellar artery, the posterior inferior cerebellar artery, the vertebral artery or the basilar artery with its branches.

SALL, Philadelphia.

ANATOMIC RELATIONS OF THE CENTRAL PATHWAYS OF THE VESTIBULAR SYSTEM. P. VAN GEHUCHTEN, Rev. d'oto-neuro-opht. **15**:321 (May) 1937.

The vestibular system is isolated from the cortical and striatal centers and from the cerebellum. Its two chief functions are to maintain the reflex equilibrium of the body and to contribute to the reflex motility of the eyes. These are rendered possible by the multiple connections of the vestibular nuclei: (1) direct connections with the spinal cord by the deiterospinal bundle and crossed connections by way of the descending fibers of the posterior longitudinal bundle and (2) homolateral and heterolateral connections with the ocular nuclei. The homolateral connections are established through the vestibulomesencephalic bundle. The crossed connections are made through the ascending vestibular fibers of the posterior longitudinal bundle and consist of fibers originating in the triangular and descending vestibular nuclei. Fibers of the posterior longitudinal bundle may be traced to the red nucleus and the thalamus. This anatomic arrangement constitutes "the primary reflex arc of the vestibular system."

The vestibular system is closely associated with the cerebellum, principally the paleocerebellum. Almost all the fibers of vestibulocerebellar association end in the roof nucleus; certain of them go to other nuclei and to the cortex of the lingula, the nodulus and the flocculus. Proprioceptive impulses from the spinal cord to the cerebellar bundle reach the vermis and are reflected through fibers of the Purkinje cells to the roof nucleus. The roof nucleus represents, therefore, a cerebellovestibular center for coordination of excitations from the labyrinth and those from the periphery.

In the higher vertebrates and in man close connections between the vestibular system and the striatum are important. The centripetal pathways may be represented by ascending fibers of the posterior longitudinal bundle to the thalamus and perhaps by fibers to the red nucleus and the thalamus, either directly or by the cerebellum, or even by way of the nucleus of Darkschewitsch. The centrifugal connections are less well known; it is recognized that connections exist between the globus pallidus and the perirubric region.

Afferent and efferent connections between the vestibular nuclei and the cerebral cortex seem indispensable. Stimuli received in the vestibular nuclei may reach the cortex of the frontal and parietal lobes by way of the posterior longitudinal bundle and thalamus and by the central acoustic pathway. The cortical zones probably react on the vestibular centers through Türck's bundle or the temporopontile bundle, but the actual pathway is not known. It is not certain that vestibular impressions reach the frontal lobe and the motor zone, but it is logical to assume that the motor cortex may influence the vestibular centers in the exercise of voluntary motility. Such influence may be exerted by the aberrant peduncular fibers of Dejerine, which go in part to the nuclei of the posterior longitudinal bundle and perhaps in part to the triangular nucleus.

The vestibular system is integrated with the highest mechanisms that rule automatic and voluntary motility.

DENNIS, Wagon Wheel Gap, Colo.

Basal Ganglia

POSTENCEPHALITIC TORSION SPASM. DIVRY and E. EVRARD, J. belge de neurol. et de psychiat. **37**:179 (March) 1937.

Divry and Evrard describe the pathologic changes in the case of a feeble-minded boy aged 17, who had had torsion spasm of the neck since the age of 13.

He had also shown rigidity of the spine and of the upper extremities, especially on the left, and, to a lesser extent, of the lower extremities. The clinical picture resembled that of decerebrate rigidity; tonic neck reflexes were present.

Study of the brain showed evidences of parenchymatous degeneration and glial scarring in the substantia nigra, with remnants of previous perivascular infiltration. There were Alzheimer cell changes in the substantia nigra and the quadrigeminal bodies. The pathologic changes involved the pallidum and infundibulum, but the maximal change was in the mesencephalon. The authors believe that the process is encephalitic, but state that it is unusual for one to find lesions so similar to those observed in postencephalitic parkinsonism without clinical signs of parkinsonism. They stress the correlation between the lesions in the mesencephalon and the symptoms of decerebrate rigidity and call attention to the fact that mental deterioration may follow a postencephalitic torsion spasm.

WAGGONER, Ann Arbor, Mich.

A CASE OF HEMICHOREA ASSOCIATED WITH A LESION OF THE CAUDATE NUCLEUS. A. AUSTREGESILO and A. BORGES-FORTE, Rev. neurol. **67**:477, 1937.

Austregesilo and Borges-Forte report a case of hemichorea limited to the left upper extremity and to the head and face in a woman aged 70. On examination two years after the onset the choreic movements were intense. Static equilibrium was insecure in the upright and seated positions. The movements ceased at rest and were replaced by generalized hypotonia. There were no signs of pyramidal disturbance. The patient was profoundly demented, indifferent to surroundings, puerile and completely disoriented. There was arterial hypertension. The spinal fluid was normal. Death occurred three years after onset of the chorea. A small area of softening was observed in the middle and superior thirds of the right caudate nucleus. There were extensive demyelination and loss of ganglion cells outside the softening, in the right caudate nucleus and putamen, and also in the left caudate nucleus. Extensive rarefaction and atrophy of ganglion cells were present in the pallidum on both sides and in the substantia nigra. The authors conclude that postapoplectic chorea is a striopallidal syndrome. They agree with C. Vogt, Foerster and others that somatotopic localization is present in the striatum—the head of the caudate nucleus corresponding to the head, the middle third to the upper extremity and the posterior third to the lower extremity. The chorea affects the side opposite the lesion.

LIBER, New York.

PATHOLOGIC LESIONS IN THE OPTIC THALAMUS: I. RELATION TO SPECIAL VASCULAR REGIONS; II. SIMULTANEOUS SOFTENING OF SEVERAL VASCULAR REGIONS (ESPECIALLY THAT OF CHOROID ARTERY) AND MALACIAS OF INDETERMINATE THALAMIC VASCULAR REGIONS; CORTICAL AND SUPRATHALAMIC MALACIAS WITH THALAMIC SYMPTOMATOLOGY; III. RELATION OF SENSORY AND ANOSOGNOSTIC DISTURBANCES TO THALAMIC FOCI; COMPARISON WITH CORRESPONDING PHENOMENA ASSOCIATED WITH SUPRATHALAMIC AND CORTICAL FOCI; IV. MOTOR DISTURBANCES. PAUL SCHUSTER, Arch. f. Psychiat. **105**:358 (Sept.); 550 (Nov.) 1936; **106**:13 (Dec.) 1936; **106**:201 (Jan.) 1937.

In these four contributions Schuster reports the results of an intensive clinicopathologic investigation of thirty-seven cases. In twenty-six of these the pathologic foci were in the thalamus (twenty-one were studied microscopically and five macroscopically). In eleven other cases the clinical picture indicated involvement of the thalamus, but pathologic studies revealed disease with a suprathalamic localization. The lesions were practically all softenings, but fresh hemorrhages were also observed.

In the first contribution Schuster proposes a subdivision of the thalamus into five regions, depending on the vascular supply: (1) the area supplied by the

thalamogeniculate artery, comprising the posterolateral part of the thalamus and reaching on the temporal side only to about one-half the height of the thalamus; (2) the area supplied by the thalamoperforate artery, comprising the posteromedial part and the hypothalamic region; (3) the area supplied by the tuberothalamic artery, comprising the anteromedial part; (4) the area supplied by the lenticulo-optic artery, comprising the upper and lateral portions, and (5) the area supplied by the anterior and posterior choroid arteries, comprising the inner and upper portions of the thalamus and the main portion of the pulvinar. All the cases reported in this contribution show restriction of the lesions to one or another of these areas.

The second contribution deals with cases in which two or more of these areas were affected simultaneously, as well as with those in which thalamic symptoms were produced by lesions in the cortex and other suprathalamic regions.

In the third contribution an attempt is made to correlate the symptoms reported in the previous two contributions and to relate them to the function of the thalamus and the areas associated with it. In this contribution the discussion is limited to sensory anosognostic disturbances associated both with thalamic and with suprathalamic lesions.

In the fourth contribution is undertaken a similar discussion of general motor disturbances, the so-called thalamic hand, disturbances of emotional expression, dysarthria, vegetative dysfunctions, disturbances in movements of the eyes and the general relationship of the thalamus to psychic functions.

The most important conclusions are summarized as follows: 1. Thalamic lesions may occur without causing sensory disturbances. 2. Superficial sensation of each half of the body is usually related to both thalami, but deep sensation is related to the contralateral thalamus. 3. Diseases of the thalamus in which there are similar disturbances in sensation are not necessarily due to lesions in the same locus, since disturbances of the different qualities of sensation cannot be strictly localized in the thalamus. 4. The syndrome of spontaneous pains and hyperpathia may occur as the result of different types of lesions; this syndrome is found to be related chiefly to the lateral parts of the nucleus lateralis, more frequently perhaps when the nucleus medialis is diseased at the same time. 5. There is probably a close relationship of hyperpathia to the sympathetic system. 6. In man, in contradistinction to lower animals, the medial nucleus seems to have no relationship to cerebrospinal sensation. 7. With some cortical lesions one may find forms and combinations of sensory disturbances which are otherwise associated with purely thalamic lesions. 8. Generalized psychic hyperesthesia seems to occur more frequently with thalamic than with cortical hyperpathia. 9. The thalamocortical system represents an apparatus which functions as a unit. 10. The syndrome of anosognosia can occur in connection with purely thalamic foci of the right side and is usually accompanied by hyperpathia. 11. Thalamic hemiplegias are most frequently of the hypotonic type. 12. Ataxia need not be a constant concomitant of the thalamic picture and may occur without any disturbance of deep sensation. 13. The tremor-like motor disturbances that occur with thalamic foci must be differentiated from choreo-athetoid movements, since the former usually manifest themselves during movement whereas the latter can occur also during rest. In both types of disturbances one practically always sees lesions in the rubrothalamic radiations. In the case of choreo-athetoid movements, however, there are usually in addition lesions of the striatum or striothalamic regions. This leads one to the conclusion that the tremor-like disturbance of thalamic origin is related to disease of the rubrothalamic tracts, whereas choreo-athetoid movements are associated with a break in the striothalamic connections. 14. The position of the fingers of the so-called thalamus hand is not always the same, but is distinguishable from that seen in ordinary hemiplegia; this disturbance is practically always associated with choreo-athetoid movements and is found in about one fourth of all cases of thalamic lesions. Since it is accompanied by choreo-athetoid movements, the name should be "striothalamic hand." Usually some voluntary movement is preserved in this disturbance of the hand. 15. One can find no incontrovertible

proof that the thalamus is directly related to mimetric innervation. 16. Regulation by the thalamus of the voice, the bladder, rectal evacuation and vasomotor phenomena is probable. 17. In most thalamic motor disturbances (including the "thalamic hand") one can find evidence that each thalamus influences both sides of the body. 18. When choreo-athetoid disturbances of thalamic origin occur early in childhood they usually are permanent; if the onset is in later life they frequently disappear.

MALAMUD, Iowa City.

Diseases of Skull and Vertebrae

PAINFUL COCCYX. G. A. DUNCAN, Arch. Surg. **34**:1088 (June) 1937.

Duncan states that from 1924 to 1934 278 patients (97 per cent of whom were women) were admitted to the outpatient department of the New York Orthopaedic Dispensary and Hospital with the complaint of pain in the coccyx. The average age was 34 years. The most common cause of the fall in this group of patients was slipping on an icy pavement and landing in the sitting position. The interval between the time of injury and the patient's admission to the hospital for treatment varied from three days to six months. Nonoperative treatment consisted of improving the patient's posture, having her sit erect and pull the buttocks in under the trunk. This took the superincumbent weight of the body off the coccyx and caused the soft parts surrounding the coccyx to act as a natural cushion. Hot sitz baths for from twenty to thirty minutes twice each day proved of value. Constipation, when present, was relieved by suitable laxatives. Local massage proved beneficial to many of the patients. Steady but firm stretching of the coccyx posteriorly was exerted for several consecutive visits, with relief from pain. This is done to overcome the spasticity of the muscles having their insertion on the coccyx and to prevent the formation of adhesions and contractures in the sacrococcygeal joint and the surrounding coccygeal structures. Local injections of from 70 to 80 per cent alcohol, physiologic solution of sodium chloride or 2 per cent solution of procaine hydrochloride gave only transient relief or were unsatisfactory. Of the 248 patients treated by nonoperative methods, 54 were examined from one to four years after the onset of coccygeal pain. Only 2 continued to complain of a painful or tender coccyx. Fusion of the sacrococcygeal and intercoccygeal joints had taken place in a large number of the patients, and in the rest there was limited motion. This limitation of motion in the coccygeal joints, coeval with cessation of pain, is additional evidence that the coccygeal pain came from a lesion of the joint. Injection of alcohol about the coccyx may not cause degeneration of the coccygeal nerves, but by causing scar tissue to form it may so limit motion of the coccyx that the pain is diminished or cured. In the 2 patients who continued to complain of coccygeal pain, motion at the sacrococcygeal joint caused an identical pain. Relief from pain was experienced by 36 of the 54 patients within one month after the injury, by 11 within two months and by 5 within six months. The results seem to indicate that the nonoperative form of treatment should be tried for a period of six months before operative resection of the coccyx is resorted to.

Thirty of the patients in the total group had operative resection of the coccyx. The average duration of their symptoms before resection of the coccyx was eighteen months. Patients were followed on an average for two years after coccygectomy. Twenty-two of these patients were relieved completely from coccygeal pain; 3 had only partial relief from pain, and 5 were unimproved.

EDITOR'S ABSTRACT. [J. A. M. A.]

PATHOLOGIC CONDITIONS OF THE SPINE: PAINFUL DISTURBANCES OF INTERVERTEBRAL FORAMINA. L. A. HADLEY, J. A. M. A. **110**:275 (Jan. 22) 1938.

Preliminary to a consideration of disturbances of the intervertebral foramina, Hadley reviews briefly the anatomic and pathologic characteristics of the intervertebral disk. Two distinct types of pathologic change in the intervertebral disk produce thinning of this structure. Thinning allows the vertebral bodies to

approach each other, so that apophysial subluxation or slipping of the posterior joints may result. Pain may be caused by bony impingement of the tips of the subluxated articular processes or by constriction of the intervertebral foramina. Extreme lordosis favors subluxation of the posterior joints. Bony exostoses in the midcervical region produce encroachment on the foramina. Angulation of the cervical part of the spine is traumatic. Fusion of adjacent segments of this portion of the spine is common, and may be congenital or acquired. In addition to the characteristic roentgen appearance, there are pain and tenderness to deep pressure in the neck or back, with restriction of motion and muscular spasm. Muscular spasm tends to maintain the overriding, causing continuance of the pain. Referred symptoms are those of radiculitis; the pain corresponds in distribution to that of the nerve root involved, the principal divisions being brachial, intercostal, abdominal and sciatic. There may be disturbance of the reflexes, muscular atrophy or Dejerine's sign, that is, pain of nerve root distribution on coughing, sneezing or bearing down. The nerve roots are painful to deep pressure along the spine. Homolateral or contralateral scoliosis may be present.

EDITOR'S ABSTRACT.

Society Transactions

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

HENRY A. REYE, M.D., *President, in the Chair*

Regular Meeting, Nov. 18, 1937

RELATION OF ALCOHOLISM TO DEMENTIA PARALYTICA. DR. WILLIAM H. KELLY, Pontiac, Mich.

A surprisingly large number of young persons with syphilis and a history of alcoholism have been observed in recent years at the Pontiac State Hospital; the earlier the development of a psychosis the more outstanding had been the use of alcohol. Many of these patients were seen in the outpatient clinic, after arrest for drunkenness, because they had been acting in a "queer" manner. Examination, supported by laboratory studies, revealed dementia paralytica. Fifty-six patients with syphilis were admitted to the Pontiac State Hospital between June 1935 and June 1937. Of these, the condition of 48 was diagnosed as dementia paralytica from clinical and laboratory findings; 6 had been treated; no patient with the tabetic form of dementia paralytica or meningovascular syphilis was included in compiling the statistics.

Dementia paralytica is a diffuse inflammatory and degenerative condition affecting mainly the cortex; the lesions consist of perivascular infiltration, hyaline degeneration and obliteration of vessels and degenerative changes secondary to anoxemia produced by endarteritis. Ischemic changes occur when local circulation has been arrested for about six hours. Cells in the second and third pyramidal layers show first swelling and then atrophy; pericellular encrustation of glia cells, revascularization and replacement of parenchyma by new mesodermal tissue follow. These changes occur principally in the frontal lobes, to some extent in the temporal lobes and rarely in the parietal or occipital lobes. In alcoholism the change is edema of the brain associated with chromatolysis and eccentric displacement of the nuclei of the nerve cells, with minor pericellular changes in the glia cells, which are greatest in association with delirium tremens and the Korsakoff psychosis. There is acute swelling, and there may be vacuolation of protoplasm, but not destruction of the nerve cells. The vacuolation is the result of changes in cell lipoids, which occur when the alcohol reaches a concentration in the blood of from 0.15 to 0.17 per cent. The softening or "pseudomalacia" associated with alcoholism may be seen largely in the corpora mamillaria, the cortex and the corpus striatum.

Because of the rapid improvement noted in these patients, I believe that the pathologic changes may have affected the meninges and the immediately subjacent tissues more extensively than the parenchyma. I presume that a combination of pachymeningitis, leptomeningitis and encephalitis forms the pathologic basis for the conditions that have yielded the best results under treatment. The lack of judgment and the emotional instability observed during recovery result from atrophy of cortical cells, but are attributable to syphilis rather than to alcohol.

Tabulation of the cases in four groups reveals that therapeutic results are distinctly more favorable when a history of alcohol was present, the patient was relatively young and the cell count of the spinal fluid was relatively high. In cases in which the alcoholism was outstanding, apparent recovery was early, and the period of hospitalization was relatively short.

In summary: Both in patients with dementia paralytica and in those with alcoholism the most prominent symptoms may be moral laxity, emotional instability

and defective judgment. The changes in personality due to syphilis may initiate alcoholism, but undoubtedly the combination of syphilitic inflammatory change and changes produced by alcohol precipitates a psychosis earlier than does either condition alone and permits earlier diagnosis and treatment of the two conditions.

EFFECT OF YEARS OF OBSERVATION ON THE DIAGNOSIS OF MENTAL DISEASE. DR. WENDELL H. ROOKS, Pontiac, Mich.

Not infrequently, the classification of mental diseases has required revision, particularly in cases in which the period of observation prior to admission was limited to a few weeks or a few months. The records of all patients in the Pontiac State Hospital have been reviewed to determine the number for whom a change of classification was made or is indicated. A review of the histories revealed, first, that many patients who had long been hospitalized presented a picture no longer typical of anything except possibly a segregation psychosis. The person who has long been dependent on a hospital environment has lost incentive to make new contacts with the realities of society and has suffered diminution in activity of the original delusional content. The physiologic processes associated with age have often made it difficult to determine the character of the past psychosis. Many former terms are now obsolete; this in itself constitutes ground for revision of classification.

The present review covers about 1,200 cases of patients admitted between 1890 and 1931 who are now resident in the institution. For 183 patients a new classification has been considered proper. Of these, the condition of 56 women and 25 men should now be classified as dementia praecox which was originally classified as one of the following: manic-depressive state (28 women and 6 men); hysterical state (16 women); primary dementia (8 women and 4 men), and paranoid condition (4 men). Each of the following diagnoses was similarly revised in 1 or 2 instances each: paranoid state; primary delusional insanity; systematic paranoid condition; psychopathic state; psychopathic condition; constitutional psychopathic state; constitutional psychopathic inferiority with episodes; acute confusional episode; imbecility; psychosis with mental deficiency; dementia paralytica; psychosis associated with tumor of the brain; psychosis associated with undetermined organic disease; melancholia; psychoneurosis; psychoneurotic state; undetermined psychoneurotic condition, and no psychosis. The condition of 13 men and 8 women now classified as manic-depressive psychosis once bore one of the following labels: dementia praecox; alcoholic hallucinosis; constitutional psychopathic state; anxiety state; paranoid state, and intoxication without psychosis. In several cases paranoia was once otherwise classified. Many patients admitted as psychotic were found not to be; some were epileptic or mentally defective.

Certain patients for whom there were multiple diagnoses deserve attention. A woman who had been admitted to another state hospital at the age of 13 as having hysteria and presenting a behavior problem was later paroled and then recommitted with a classification of the disorder as hebephrenic dementia praecox; this was later revised to manic-depressive psychosis, and still later to hebephrenic dementia praecox. After she had been paroled and recommitted a second time, the diagnosis of constitutional psychopathic inferiority without psychosis, and, finally, psychopathic personality without psychosis, was made. The condition of a man in an institution in New York was diagnosed there as dementia paralytica, of cerebral type; then, after his transfer to another institution, as constitutional psychopathic inferiority with acute hallucinosis, and later, at another institution as paranoia; the patient has now been resident at the Pontiac State Hospital since 1927, and the disease is, I think, properly regarded as paranoid dementia praecox. In the case of another man the disease was classified as dementia praecox, first of simple and later of paranoid type, then as psychoneurosis, later as hysteria and still later as a schizophrenic process; it is now definitely diagnosed as deteriorating dementia praecox. A condition in a woman which was originally diagnosed as a postencephalitic syndrome was finally judged to be dementia praecox. Another patient whose disease was originally diagnosed as a postencephalitic change

in personality was studied at the State Psychopathic Hospital, Ann Arbor, Mich.; there, a classification was made of undiagnosed psychosis and mental deficiency, with compulsive neurotic and hysterical reactions; ultimately, at this hospital the diagnosis of a postencephalitic syndrome was made. More definitely belonging in the organic group was the disorder in a girl, one of twins, who was admitted to this institution with a history of social delinquency and disturbances of gait which had been responsible for repeated arrests for "intoxication." The first classification was that of intelligence of moron grade without psychosis; subsequent progressive increase of choreiform movements led to a provisional diagnosis of Huntington's chorea. This was more firmly established by a study of other siblings, including the patient's twin brother and another set of twins, whose disorders had variously been classified as encephalitis, parkinsonian syndrome, myasthenia gravis and cerebrospinal syphilis of dementia paralytic type. Another woman, aged 30, after tonsillectomy showed mental symptoms suggestive of schizophrenia; the condition was so classified until increasing neurologic changes led to a diagnosis of progressive lenticular degeneration.

The 1,200 cases reviewed offer an average example of the classifications in many state hospitals, and these statistics form the basis of state and government records. With the evidence presented showing how observation over a period of years may influence the classification of cases of mental disease, one may question the accuracy of present statistics. It is possible that differences of opinion may exist as to the meaning of present diagnostic terms or the essentials necessary in an individual case to justify any one type of classification. More important is the possibility that there are definite relationships between certain mental states, which are not sufficiently recognized or emphasized in studies of cases and descriptions of disease and thus not indicated in the diagnoses. It may also be necessary to invent new terms to interpret the findings or to cover the various changes that occur in an individual case of mental disease.

COMPARISON OF OLD AND MODERN TREATMENTS OF DEMENTIA PARALYTICA OVER A PERIOD OF TWENTY-TWO YEARS. DR. O. R. MACKENZIE, Pontiac, Mich.

Although the method of Wagner von Jauregg in treating dementia paralytica with malaria is still favored in Europe, some American centers have indicated a preference for artificial hyperpyrexia induced by the high frequency current. During the past eleven years, treatment of dementia paralytica with malaria and intensive postmalarial chemotherapy as a routine has been especially satisfactory for the stage of advancement of the disease seen in patients admitted to a state hospital. The Pontiac State Hospital was the first institution in Michigan to use malaria as an adjunct to the treatment of dementia paralytica. As eleven years of continued success have elapsed, my associates and I now feel justified in reporting the results.

Hyperpyrexia by inoculation with malarial organisms is the method of choice because no special equipment and no trained personnel other than the hospital nursing staff is required. Furthermore, overactive and uncooperative patients become amenable to the routine of the hospital while under treatment; a course of hyperpyrexia lasts no longer than four weeks, and, finally, a beneficial mononuclear reaction is produced after therapeutic malaria. Recent literature indicates that clinical and serologic relapses are less frequent after induction of malaria and chemotherapy than after electropyrexia and chemotherapy.

The disadvantages of malarial treatment are recognized. Negroes and persons of Mediterranean origin are often refractory to inoculation with the malaria organism. We have succeeded in inoculating 5 of 12 refractory patients with malaria by the use of polyvalent typhoid vaccine (250,000,000 killed organisms per cubic centimeter), according to the following method: On the first day we injected 0.25 cc. of the vaccine intramuscularly; on the second and third days, 0.25 cc. intravenously, and at the height of fever on the third day, 10 cc. of malarial blood, 5 cc. of which was given intravenously and 5 cc. intramuscularly. We are

inclined to agree with others in the statement that with accurate clinical supervision malarial treatment should not result in a mortality rate higher than 5 per cent. Disadvantages, such as secondary anemia, loss of weight and hepatic and splenic enlargement, which have been reported, did not cause difficulty in our series.

This report presents the results obtained with 856 patients during the past twenty-two years. In the first eleven years fever therapy was not used. Prior to 1919, the administration of mercury and potassium iodide in soluble and insoluble form served as a basis for treatment. This was followed in 1919 by the use of neoarsphenamine, in 1923 by that of tryparsamide and in 1926 by the present routine of inoculation with malaria and administration of tryparsamide, bismuth and red mercuric iodide. In a review of our records I find that at no time during the eleven years of chemotherapy were the results comparable in value with those recorded after the use of malaria.

The following criteria for estimation of the clinical status were based on social and economic factors: 1. "Complete arrest" or "recovery"—a remission of the psychosis with ability to return to a social and economic level comparable with that occupied before the onset of the psychosis. 2. "Incomplete arrest" or "improvement"—partially successful adaptation to society or fair adjustment in the hospital. 3. "Progressive deterioration" or "no improvement"—a failure to adjust to the routine of the hospital slowly progressive deterioration or death within five years. When the patients were thus classified, the results during the eleven year period from July 1915 to June 1926, inclusive, for 604 patients with dementia paralytica or the tabetic form of the disease were as follows: Five-tenths per cent of the patients recovered; 10.7 per cent showed improvement, and 88 per cent did not improve or died. In the second eleven year period, from July 1926 to June 1937, inclusive, treatment of 252 patients with malaria, tryparsamide, bismuth and red mercuric iodide yielded the following results: Six and three-tenths per cent of the patients recovered; 41.6 per cent showed improvement, and 52 per cent did not improve or died.

This report considers only the two most malignant forms of neurosyphilis, dementia paralytica and the tabetic form of dementia paralytica, associated with a malignant change in the spinal fluid, marked changes in personality and conduct, defects in judgment, impairment of memory and neurologic changes. In spite of this, of the malarial group it has been possible to parole 16 patients as recovered and 34 as improved; in addition, of those who have not improved sufficiently for parole or at all, 40 per cent are at present able to assist in various duties in the hospital routine. In summary, one must consider that only two forms of neurosyphilis are included; that after eleven years' experience in the treatment of dementia paralytica and the tabetic form of the disease with induction of malaria and intensive postmalarial chemotherapy it is believed that this regimen offers a high incidence of remission for institutional patients; that the percentage of patients who benefited from treatment was over four times that for the first series, and that the various disadvantages reported for malarial therapy, such as a high mortality and secondary anemia, have been practically negligible in this series.

INTESTINAL PATHOLOGIC CHANGES OBSERVED AT AUTOPSY AT THE PONTIAC STATE HOSPITAL. DR. RICHARD E. OLSEN, Pontiac, Mich.

In a series of 120 cases in which autopsy was performed at the Pontiac State Hospital there have been a number of interesting, and even bizarre, instances of pathologic changes in the intestine. These appear to be incidental to, rather than a cause or result of, mental disease. I consider that pathologic changes in the intestine are more common among patients with mental disease than among general hospital patients. Three patients were recorded as having two major intestinal conditions: A white woman aged 31 had a chronic peptic ulcer in the duodenum and tuberculous ulceration of the ileum; a white woman aged 70, a chronic peptic ulcer of the pylorus, in which there had developed a low grade adenocarcinoma, and a white man aged 66, a chronic ulcer of the lower third of the esophagus and a large perforated peptic ulcer of the pylorus. An elderly white man with

marked chronic constipation had an enormous number of pinworms throughout the colon. A white man aged 71 had carcinoma of the lesser curvature of the stomach, with metastases to the regional lymph nodes. Another white man aged 63 had carcinoma of the cardiac portion of the stomach with extensive metastases. Two patients had megacolon, probably of congenital origin—a white woman aged 82, with no definite symptomatology, and a white man aged 38, who died suddenly after distention of the colon from an acute obstruction at the rectosigmoid juncture.

NEW YORK NEUROLOGICAL SOCIETY

MOSES KESCHNER, M.D., *President, in the Chair*

Regular Meeting, Feb. 1, 1938

THE OPIUM ADDICT AND HIS TREATMENT. DR. LAWRENCE KOLB, Lexington, Ky.

Most addicts are recruited from among unstable persons and suffer from the weaknesses and delinquencies common to this type, plus a certain amount of moral deterioration brought about by furtive concealment of the habit, the evil associations they are compelled to keep, the strong physical impulse they all have to get the drug at any cost in order to prevent suffering and the mental and physical lethargy that the drug produces. It is difficult, however, to separate the original psychopathic and delinquent tendencies from those produced by the habit, and as a result the effect of original instability that leads to delinquency is often confused with the effect of the habit.

The unstable addict uses opium to blot out feelings of inferiority, inadequacy and distress, and treatment depends largely on teaching him how to adjust in more healthy ways. The physical dependence produced by the continued use of opium, however, is a condition peculiar to the drug and, as evidenced by the symptoms produced by abstinence, is a spectacular thing. For this reason, most attention has been given to treatment during withdrawal.

Little is known of the fundamental mechanism of addiction to opium, but a number of treatments based on theories concerning it have been advanced. Without exception, these treatments have been either harmful or useless. In no instance has the author taken the trouble to use controls in order to test whether his treatment was better than others or than none at all; in every instance the author has apparently failed to take account of three simple facts that must be considered in evaluating the merits of a treatment: First, addicts with the same degree of habit vary in the intensity of their reaction to withdrawal; second, only about 20 per cent of addicts who come for treatment have habits sufficiently strong to justify their inclusion in a program designed to test the value of a cure, and, third, all addicts from whom opium is withdrawn quickly recover from the symptoms of withdrawal regardless, and in spite, of other treatment to which they are subjected, provided the treatment contains nothing that is harmful.

The scopolamine treatment exemplifies best how addicts survive the period of withdrawal and recover in spite of vicious medication. The purgation, the strychnine and the pilocarpine used in this treatment add to symptoms already present and to the distress caused by the large doses of scopolamine.

Other harmful or useless treatments, some of which have been widely employed, are those with belladonna, narcosan (a proprietary preparation of plant extractives), bromide, sodium thiocyanate, Modinos' autogenous serum (blister treatment), rossium and insulin. The last two methods are the newest and deserve special mention.

The anaphylactic theory on which the rossium treatment is based contains three remarkable errors; namely, that the symptoms of withdrawal are similar to those of anaphylactic shock, that addiction starts suddenly at about the twen-

tieth day of continued use of morphine and that a cured addict will have the addiction reestablished by a minute dose of morphine and will have all the symptoms of withdrawal unless administration of the drug is continued.

The insulin treatment is based on the following theory: The cells are normally stimulated by a hormone (epinephrine) which attaches itself to a cell receptor; morphine replaces the epinephrine by attaching itself to the receptor, causing sedation and euphoria; morphine stimulates the formation of other receptors, and when it is withdrawn the stimulating hormone combines with the increased number of cell receptors and overstimulates the cells, causing the symptoms of withdrawal. Insulin, when given in sufficient quantities, combines with the receptors, thereby excluding the stimulating hormone and preventing the symptoms.

In describing his theory and the technic of withdrawal, Sakel states that during withdrawal there is hypoglycemia, due to the fact that epinephrine stimulates the cells and is not available for metabolism. This part of the theory seems to be wrong, for my colleagues and I have found on the basis of examination of hundreds of patients at the United States Narcotic Farm, Lexington, Ky., that not hypoglycemia but hyperglycemia is invariably a part of the withdrawal picture. Neither insulin nor rossium has had any effect on the withdrawal symptoms of patients treated at Lexington.

The method that has given us the best results is rapid withdrawal in from four to ten days by the use of morphine or codeine or both in small doses. Restlessness is reduced by warm baths for ten minutes three times a day, and patients who do not eat well are given 1,000 cc. of a 5 per cent solution of dextrose intravenously as often as three times a day. Diarrhea is controlled by 5 grains (0.324 Gm.) of bismuth subcarbonate, and sleeplessness, by administration of from 12 to 20 cc. of paraldehyde in olive oil by rectum at bedtime. Sodium bromide in small doses is given in some cases for three days, but no longer. Under this treatment the acute symptoms quickly subside, and the patient begins to gain weight four days after the last dose of narcotic. An attempt is then made to build up more healthy habits of adjustment by work and recreation that keep the patient busy during his waking hours. Treatment for several months is necessary to effect this and to give the patient time to overcome the needle habit.

Relief from oncoming distress and restlessness, due to dying down of the effect of the last dose, has been brought about by an injection so often over a period of years that any distress is immediately associated in the mind of an addict with the use of a needle; some will use a needle even though there is no morphine to inject. The physical and mental upsets during the course of treatment to which the addict adjusts without the use of a needle do much toward breaking the association between the needle and pain and in curing the needle habit.

Special psychotherapy, not psychoanalytic, is important and is given to a selected few. We have not found that latent homosexuality is at the root of the trouble in any number of patients. Psychotherapy consists of discussing with the patient his life and problems, and suggestion forms a part of it. It is designed to induce the patient to understand his own weaknesses so that he can solve his problems normally by facing and fighting them in the open, instead of by evasion. Sermonizing is useless. The addict knows he has wasted part of his life and wants to be shown how to stop using opium so that he can save the rest.

DISCUSSION

DR. S. W. HAMILTON, White Plains, N. Y. (by invitation): The few addicts in every hospital for mental disease, private or public, are usually considered nuisances because they must be managed along lines different from those for most patients in such hospitals. There are many addicts who do not come to hospitals for the mentally ill because these hospitals do not want them; there are also legal barriers. In upstate New York these barriers are not so high, and some addicts are certified as mentally sick; in the city of New York, however, they are to be found in penal institutions. I have no doubt that much good clinical work has been done in the New York City Penitentiary. The time has come when the

Federal Government is taking the matter seriously in hand. When one goes to the narcotic farm at Lexington, one finds a fine institution. If a patient takes pride in any place to which he has been brought for his difficulties it may well be here. Dr. Kolb did not plan this structure; he found that those who had planned it had thought largely in terms of prison architecture. I was pleased to find that Dr. Kolb considered it his responsibility to demonstrate that prison features are not necessary on any considerable scale. He is keeping patients as far as possible out of the cell block. The plan of the undertaking at Lexington is impressive. It indicates a determination, a fine purpose, on the part of the United States Public Health Service to be of use to this group of patients. The organization of the institution is quite as impressive. The farm started, Dr. Kolb tells me, with about 40 patients; the high point thus far has been a little over 1,000, and the number is now over 900. There are 13 physicians; 2 psychologists; a laboratory technician, biochemists and physicists, with attendants assigned to help them; 3 dentists (the care of the mouth is important in addicts), and a personnel of 245. More impressive than numbers is the character of the men who have been assembled in this institution, from the medical officer in charge down through the staff.

At Lexington, the staff are making special studies of metabolism before, during and after the time that the patient is taking drugs, as well as encephalographic studies and determinations; of the lactic acid and phosphorus contents and other chemical constituents; at the same time, they are carrying on careful psychiatric investigations. This, therefore, is a place not only for fine treatment but for research.

DR. WALTER BROMBERG (by invitation): I had the opportunity of hearing this paper at the meeting of the American Psychiatric Association in 1937; I still feel that it is the fairest, most scientific and accurate review of the treatment of drug addicts yet presented. I was particularly impressed with the objective attitude of the workers associated with Dr. Kolb in a field which is apt to be overrun with buoyant claims and slight performances. It must be acknowledged that this difficulty is due in part to the inherent difficulties in the problem, in which subjective and objective reactions are so intertwined that careful analysis can easily be discouraged. If one adds to this the fact that drug addicts, although cured after each period of treatment, more often than not relapse into the habit, one begins to see the complexity of the problem of therapy for drug addiction.

There is nothing from my experiences with drug addicts that I can add to the discussion of the technic or methods mentioned by Dr. Kolb. At the psychiatric clinic of the Court of General Sessions, my associates and I see drug addicts who are convicted felons and who are there for crimes other than the use of selling of habit-forming drugs. The vast majority of users of drugs who are arrested or give themselves up for treatment pass through the Court of Special Sessions of New York County and are sent to the New York City Penitentiary for treatment. According to Dr. P. H. Amoroso, head of the medical unit of the department of correction, 941 drug addicts were treated in the New York City Penitentiary during 1937, and a total of 1,300 persons who had a history of drug addiction were admitted during that year.

In contrast to this is the fact that only 34 persons with the diagnosis of drug addiction were convicted in the Court of General Sessions during the same period and hence passed through the psychiatric clinic. In the clinic we see about 2,600 convicted felons a year. From these figures one obtains an idea of the relative frequency of drug addiction among criminals. It is obvious that drug addiction is a small factor in the commission of felonious offenses.

In view of the common belief in the relationship between violent crime and drugs, it may be worth while to give an idea of the types of crime committed by the 195 persons for whom a diagnosis of drug addiction has been made in the six years of the clinic's existence. Of the 195 addicts, 50, the largest group, were convicted of burglary; 44, of grand larceny; 12, of robbery; 11, of assault, and

2, of homicide. There were no convictions for sexual offenses by the Court of General Sessions of New York County among any of the persons for whom we made the diagnosis of drug addiction.

The problem of stimulation of aggressive and sexual instincts by drugs is of great importance. The reading public has been impressed from the time of Edgar Allan Poe and Fitz Hugh Ludlow with the crime-stimulating quality of drugs. Since almost all the offenders had been convicted of previous offenses and had been addicts for several years, it would be more accurate to ascertain whether in their past there were any convictions for sexual offenses or crimes involving violence. Some of these offenders had been arrested—1 had a history of 52 arrests, and the majority, from 5 to 10 arrests. As compared with the records for other arrested persons, those for drug addicts were unusually long. Of the entire number of arrests—about 1,600 in all—we found only 4 previous arrests for sexual offenses (2 for impairing morals of a minor, 1 for sodomy and 1 for rape), 1 for murder, 10 for robbery and 2 for assault.

What is the significance of these figures? They mean that drug addiction is by far a greater medical and sociopsychologic than a criminologic problem. Experts in the field of practical pathology have emphasized the importance of treating drug addicts without arresting them, and others have urged the American Prison Association to recommend that addicts be treated without first being arrested. Drug addiction is, like prostitution, a sociopsychologic problem and should be handled with due regard to its psychiatric implications.

It is acknowledged that treatment of drug addiction must involve rehabilitation. As Dr. Kolb has pointed out, this should be an essential part of the program of hospital treatment of these patients. Once they return to their environment, however, the chances that the habit will recur are almost 100 per cent. Hence, a rehabilitation plan for drug addiction presents many grave problems. Not the least of these is the question of life outside the institution, with its opportunities for using drugs to support the needs of a weak ego. I have been thinking for some time of the advisability of bringing knowledge of drug addiction before the public. With the method of mental hygiene, the question of drug addiction should be stripped of its fantasy and mysticism. Certainly, it seems that this type of social hygiene, with a page borrowed from the newer methods of fighting syphilis, would be well worth the effort.

Dr. Israel Strauss: It has been a pleasure to listen to a "debunking" demonstration this evening. I was a member of the Mayor's committee appointed particularly for the purpose of studying narcosan; like Dr. Kolb, my associates and I found that narcosan has no value whatever. Further, we concluded that the matter of withdrawal was practically of no significance, that rapid withdrawal, by which we meant withdrawal within a few days, might make a person feel a little more uncomfortable than slow withdrawal but that it was immaterial in what way one withdraws the drug—the patient can recover from the withdrawal symptoms and be well for the time. We were dealing with persons who were users of the drug and were sent to us by the courts. It is interesting that many of these persons came to have the addiction cured for a specific reason: It was costing too much to get the amount of drug they needed; they wanted a reduction to amounts which they could afford to buy. We were asked for the solution of this problem. Should an institution be started in New York State for the purpose of curing drug addiction? I do not know whether the Federal Government was contemplating this at the time. We concluded that an institution in which the class of patients with whom we were dealing could be treated would have to be extremely well guarded, for we found that even though addicts are well guarded in the Bellevue Hospital one or two managed to smuggle in the drugs; that, I understand, is the case at most institutions. We concluded that if the drug is withdrawn and the patient is rehabilitated, a factor of the greatest importance remains, that is, the psychologic factor. We asserted that every drug addict is in a measure a psychiatric problem and that breaking off the drug is the least important part of the technic. After he is discharged from the institution, how is he to be returned to an environment in which he will be able to make adjust-

ments to his conflicts? That seemed to us at the time to be an almost hopeless proposition. We came to the conclusion that drug addiction is not the great curse that Hobson and propagandists and societies with similar gospels had promulgated, and we expressed the belief that there are many persons using morphine who are well adapted to adjust in life. There is a certain group, of course, who are victims of the habit; as Dr. Bromberg has emphasized, however, criminals are not recruited from the class of drug addicts, and we wondered how much good an institution would do. Some of us said that the best way to cure drug addiction is to prevent acquisition of the drug. There are laws to prevent traffic in opium and heroin (diacetylmorphine), to no avail. If securing, or at least traffic in, these drugs could be stopped, I think that there would be no great difficulty with the problem of drug addiction.

Dr. Kolb spoke of psychotherapy; I wonder how 11 physicians can use psychotherapy on 1,000 patients. They probably make an attempt in suitable conditions.

Does Dr. Kolb have statistics on how many addicts who have been discharged remained free from the addiction? I think that if these patients are followed, it will be shown whether or not this magnificent work is of great benefit.

Dr. Sam Parker, Brooklyn (by invitation): I wish to ask Dr. Kolb if he can answer two questions in his closing remarks: First, to what extent has he observed the incidence of avitaminosis among the drug addicts, and in what way has the occurrence of these conditions altered or affected the treatment? Second, can he, briefly, consider the incidence of psychoses among the patients treated at Lexington and in what way these psychoses affect or alter the treatment used?

Dr. Lawrence Kolb: I wish to thank Drs. Hamilton, Bromberg and Strauss for what they have said about our work in the hospital at Lexington. I agree with Dr. Bromberg that the association between criminality and drug addiction is unimportant. After the Harrison Narcotic Law was passed, thousands of persons were sent to prison because of violations of the act; some fanatics and uncritical physicians, observing the increased number of addicts in the prison population, began to write of the terrrible association between drug addiction and crime, losing sight of the fact that the increase in prison population was due to the new law. About 97 per cent of the prison population at Lexington are there because of conviction for violation of a narcotic law.

The report of the Mayor's committee of which Dr. Strauss spoke is, in my opinion, one of the best articles that has been written on drug addiction. It did a great deal of "debunking," but the information contained in it does not seem to have been disseminated widely.

Dr. Strauss asked about the number of permanent cures. Some physicians and many police officials have an idea that drug addiction cannot be cured. Persons with this opinion have observed that certain addicts return time and again, either for treatment or to the courts; they forget all about the hundreds of addicts who are permanently cured and never come to their attention again. I know personally of physicians and others who have been cured for years, and we at Lexington still hear from a number of patients who were cured there. Some of these have psychopathic traits which, in the face of unusual stress, may cause them to return to narcotics later, but many of our patients become adjusted permanently. The proportion of permanent cures may be small because we are working at Lexington with the residue of a group that has often been worked over before, so that the patients with the more hopeful prognosis have been eliminated by cure. Many of our patients have been in institutions a number of times. They started in childhood with psychopathic traits that have been intensified by environmental influence, so that now there is small hope of influencing the condition on which the addiction depends; others who came into addiction late in life and show less serious deviation from the normal can be permanently benefited by the time element in treatment combined with psychotherapy and other measures. However, we cannot use much psychotherapy with 900 patients. Our policy is to select from the more intelligent patients those who offer the best prospects for benefit by intensive psychotherapy.

Also, our staff of nurses is instructed in the fundamentals of psychotherapy, so that they are able to give treatment of a less intensive kind to a large number of the patients.

As to Dr. Parker's question: We have not had any evidence of avitaminosis as a factor in drug addiction. Some addicts are terribly emaciated when they come for treatment. This is because they have been unable to provide themselves with food and support a drug habit at the same time. If they can secure food they will eat it, but even those who become emaciated do not acquire neuritis or deficiency diseases as do those who substitute a substance like alcohol for vitamin-containing foods.

The incidence of psychoses among addicts is small, and when a psychosis occurs we do not attribute it to opium. I have grave doubts whether the continued use of opium ever causes a person to become psychotic. On the other hand, I am inclined to believe that some inferior persons have been saved from psychoses by taking the drug. During withdrawal there is occasionally a mild psychotic episode, lasting a week or less, and I have seen several neurotic addicts who had been addicted for many years pass into a hypomanic state of several months' duration when the drug was withdrawn.

OBSESSIVE RUMINATIVE TENDENCIES FOLLOWING INTERRUPTION OF THE FRONTAL ASSOCIATION PATHWAYS. DR. WALTER FREEMAN and DR. JAMES W. WATTS, Washington, D. C. (by invitation).

With a small series of patients presenting prolonged obsessive ruminative tendencies, a certain degree of success has been attained by interruption of the subcortical association pathways of the frontal lobe. The intellectual functions are relatively little impaired. There are emotional flattening, diminution of affect, interruption of the obsessive character of the ideas, reduction in blocking and vanquishing of abnormal self consciousness, which enable these patients to lead a more comfortable existence and, in some cases, to resume activity of a fairly productive nature. The patients have been observed for a sufficiently prolonged period so that the operative shock or suggestive therapy is scarcely to be considered of importance in explaining the outcome. The patients who show the best results react in a dull, retarded way for several days, or even weeks, after the operation; undue alertness immediately after operation apparently prefaces a relapse. The progressive improvement over a period of months seems to indicate that once the vicious circle is broken by the operation, a progressive readjustment of the whole personality is possible.

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DISCUSSION

DR. RICHARD M. BRICKNER: Drs. Freeman and Watts have studied frontal lobotomy for nearly two years, and it has been of great interest to observe their results. I have had the privilege of seeing a number of their patients after operation, among whom was the young woman with the obsession about shoes, whose case is described in the present report. When I saw her, there was no question that many of the obsessive ideas had persisted. Not much associated affect was evident at the time, although, according to her description, some affective disturbance was still present. It was also true that she was still somewhat incapacitated, but not to a degree comparable with that in the preoperative state. I have since been told that she is in a sanatorium again. The patient expressed the belief that she had improved considerably but, true to her perfectionistic colors, she laid emphasis on the symptoms which were left. Her tepid feeling for the operation and her loyalty to the remaining symptoms struck me as being themselves of obsessive nature. I doubt whether one can expect a whole manner of thinking—obsessive thinking in these cases—to be changed by a local operation of this kind; I should think that the persisting obsessive habit, applied to the postoperative result, might itself impair the value of the outcome.

The favorable outcome in this group of 4 patients with obsessions is not as striking as one would like to see, nor does it compare well with what has been gained by other patients without obsessions. Still, the passage of time after operation was of benefit to 1 patient, and it will be of value to learn what happens to patients 2 and 4. It is too early to form an opinion about patients with obsessions, such as those reported on tonight. My belief is that the procedure should be tried for relief from desperate, long-standing agitation or depression. There is little else to offer patients with such conditions. That the procedure is radical is of little significance when one thinks of the years spent in institutions and of the possibility of suicide.

It has several times been proposed that the effects of this operation are due to suggestion. I think that the observations reported tonight point strongly against this possibility, when one remembers that the obsessive ideas may be retained though the degree of anxiety is reduced.

A discusser of a paper by Drs. Freeman and Watts has even said that the operation could be carried out just as well on the hand or the foot. This attitude, which is not uncommon, bespeaks a lack of belief in the neuronal nature of thought and feeling. Evidence is continually accumulating to show that both these functions can be understood explicitly in neural terms. The observations reported tonight bear on this matter. They add to knowledge of the neuronal arrangements of intellect and its relation to feeling tone. In all the work of Drs. Freeman and Watts, the most conspicuous finding has been the diminution of anxiety and depression. It is notable that this is true of the obsessive states also, even though the obsessive ideas as such may persist. All this, it seems, fits in with the anatomic localization of the procedure.

The cortex itself is practically spared except for the leukotome hole. Probably some of the association neurons of the cortex are injured, especially the long ones, but the short association fibers are probably not included to any great degree. They lie close to the cortex itself, and it is unlikely that the leukotome could strike many of them. The fibers which are predominantly injured must be those which form the bulk of the centrum ovale. These are of two main varieties—callosal fibers and fibers which connect the cortex and the thalamus. These peduncular fibers are the only ones in compact form which are struck by the leukotome. They lie just where the leukotome is most likely to impinge to the greatest extent. There is no evidence of severe callosal damage, in the sense that I understand it. Certainly, callosal damage is not revealed in these patients by the usual intellectual difficulties and apraxic phenomena. When all the evidence is put together, it appears that the focal point of the procedure is the pathway connecting the thalamus and the cortex.

The operation evidently spares the neurons concerned with complex intellect associated with the frontal lobe, but greatly diminishes the bonds between complex intellect and feeling tone. For this reason, intellect as such is relatively unimpaired—an observation which, I believe, has been made on nearly all the patients. At the same time, feeling tone no longer seems to be linked with the obsessive ideas to any degree comparable with that in the preoperative stage. This is shown clearly by some of the patients described tonight, with their retention of the old obsessive ideas and diminution of the associated feeling tone.

The preservation of intellect is especially striking when comparison is made of patients with lobotomy and those with removal of both frontal cortices, such as a patient whom I once presented at a meeting of this society. In that patient the dissolution of complex intellect was obvious. The behavior of patients with lobotomy is totally and instructively different from that of persons in general with large, expanding frontal lesions, in whom the intellectual deficit as such is conspicuous. Lobotomy, with its cutting off of feeling tone from complex intellect, can be compared with spinal cordotomy, done for relief from pain.

DR. KURT GOLDSTEIN: Certainly every one was astonished, even shocked at first, on learning about operations of this type on persons with functional neuroses and psychoses. One has become accustomed, however, to such heroic methods. Who has seen the exceedingly dangerous condition of patients during insulin or

metrazol treatments without becoming frightened at first? Today one accepts such conditions with no particular misgivings as to danger. The heroic character of a method should not count against it. Before one uses it, however, one must be sure that no other, less dangerous, method will aid the patient. That being admitted, one must be more or less certain that the patient will be aided by the treatment. According to Dr. Freeman, there seems to be no doubt that at least some patients improved greatly in a practical way, whereas all other treatments had failed. I had the opportunity of seeing in Washington several of the patients who were treated. Although my own observation was superficial, what some of the patients told me about their condition before and after the operation was impressive. The abnormal ideas, hallucinations in one case, did not always disappear, as Dr. Freeman himself said; even then the affective attitude seemed to have changed completely, and there was marked indifference to the obsessive ideas and hallucinations. The patients were not disturbed by their thoughts; they could be insensitive to them.

There is no doubt that the main benefit of the operation lies in the diminution or loss of compulsive feelings, which the patients particularly appreciated. That is proved, too, by the fact that one of the patients in my presence spontaneously asked for a second operation because she realized that improvement had lessened several months after the first operation.

It being admitted that the operation may help in some cases in which other treatments have failed, various questions arise: 1. How is the success achieved? This question is not easily answered. The possibility of the influence of suggestion has to be carefully considered. However, I do not believe that suggestion plays a great part. First, it is known that suggestion usually does not help a patient of this type. Further, it is important that in some cases the improvement did not appear directly after the operation but developed slowly during the succeeding weeks. As Dr. Freeman reported, success attended the operation when that occurred.

2. Can one regard the improvement as due to a change in function of the brain produced by the defect? To answer this question thoroughly would necessitate a detailed discussion of the structure of compulsive neuroses and of the function of the frontal lobe. It is impossible to do either here. I wish to make a few suggestions. I think one is right in assuming that the subcortical ganglion apparatus plays a particular role in the development of compulsive phenomena. One can assume further that this apparatus is controlled by the cerebral cortex, and here, in my opinion, the frontal lobe is of special significance.

This relationship accounts for the fact that in patients with a lesion of the frontal lobe one observes a tendency to react in a compulsive manner to external stimuli. However, this does not explain the improvement in Dr. Freeman's patients. Here one observes diminution in compulsive traits by destruction of the pathways from the frontal lobe to lower mechanisms. The relationship between these parts is not simple. The frontal lobe does not simply inhibit the functions of the lower apparatus. The frontal lobe represents an intermediary link between the part of the brain the function of which is important for building normal ideas and the mechanisms which are directly affected by stimuli. The frontal lobe regulates the activity of the apparatus important for building ideas and of those important in reacting to stimuli. An important effect of this coordination is the "adequacy" of affect and impulse. One does not know in what way this relationship is disturbed to produce compulsive phenomena, but one does know that in association with lesions of the frontal lobe impulses and affect can be diminished.

A change of this kind produced by an operation would make clear the reason for the disappearance of compulsions and the increase in affective tensions. If one considers mainly the postoperative diminutions in the compulsive tensions, there arises the question: Should the patients not be treated after operation with psychotherapy? The compulsive trends in psychoneurotic persons are not primary but secondary to psychic changes in the personality. Psychotherapy is often unsuccessful with such patients because the habit fixation of the compulsive attitude prevents freeing of the personality and hinders a real fight against the obsessive

ideas. I think that psychotherapy may be helpful after operation. I consider this as important as psychotherapy after insulin treatments of schizophrenia. I wish to ask Dr. Freeman if such treatment was tried with his patients.

Finally, as Dr. Freeman reported, the patients after operation showed emotional flattening, decrease of self consciousness and euphoric symptoms, which one associates with patients having a lesion of the frontal lobe. In these symptoms one is dealing with signs of deterioration. This suggests the last question: How far does this deterioration go? How much danger is there of the development of marked deterioration? Dr. Freeman will present material later to answer this question. However, even if closer investigations show some deterioration, this should not speak against the treatment. One must counterbalance the degree of improvement measured by the removal of compulsive phenomena and the degree of deterioration of the patient's personality. Here, one is faced with a question which is always worrisome when extreme, energetic or active therapy is involved, namely, whether one is helping the patient more than damaging him. That predicament does not concern operative treatment any more than other energetic, active therapy, including psychotherapy.

DR. SMITH ELY JELLIFFE: Needless to say, one is here faced with a situation of major significance, about which one must feel one's way with circumspection.

One is asked to voice opinions about the juxtaposition of two large problems in contemporary neuropsychiatry: the significance of certain frontal association pathways—not always specifically localized—and a rough clinical syndrome of equally bewildering complexity. This clinical syndrome may be said to extend from the simplest of habitual acts to the most complex of socially accepted, hence useful ritualistic compulsions, as well as those which are useless and socially nonacceptable.

I feel incompetent to discuss the anatomic situations in detail. At the 1934 meeting of the Association for Research in Nervous and Mental Disease this was done in masterly fashion. One is here concerned not so much with the cytotectonic destruction of the prefrontal lobes—Brodmann areas, 8, 9, 10 and 11 and perhaps 45 and 47—as with the severing of a heterogeneous series of myelotectonic "switchboard wirings" that can be arrived at only inferentially in this type of procedure. At all events, in spite of this mass of uncertainties concerning structural "wiring" problems, certain definite results have been observed. These are ready for further study, with the aid of the numerous related types of lesions experimentally produced by physiologists in lower animals, up to apes. Since in none of the lower animals has there been any synthesis of complex verbalization, of social organization or of function providing for the future security of race or nation, it is apparent that one is concerned with a type of investigation in comparative sociology, if one will, the advancing stages of which are seen throughout the animal phylum.

Throughout this phylum, now extending back fully a billion years, one preeminent pattern has had survival value. It may be called by a variety of names; it insures the continuance of the race, and the darwinian tag "instinct of reproduction" is as good as any, if one will remember that by reproduction is meant not only a genital function but a function of the entire body, specifically brought to its highest levels of capacity for sublimation in the very structures one is considering here.

It is not at all strange, I believe, that the oldest of patterns of survival value should of necessity be found in the newest of structures, the prefrontal association areas. Functional aspiration brings into being precipitates of structural organization.

Dr. Brickner has aptly termed the outstanding defect a lack of capacity for planned administration. He has applied this term especially to modifications seen in various types of everyday activity and has already noted the desirability of a more searching analysis of the phyletic stages of the reproductive pattern. From one point of view, I think it not unimportant to hark back two thousand years, when, through a partial synthesis of two types of culture, a new and better cultural plateau may be said to have emerged from earlier stages. This particular

level has been termed Christianity. One need not be reminded of the fact that the ethical concepts surrounding this level are more honored in the breach than in the observance. For the mass of mankind it remains more of a wish-fulfilling ideal than a practical reality.

Dr. Strauss, at the 1934 meeting, spoke suggestively of the "localization of censorship" in the parts under consideration. I am certain this is not a faulty conception if one means by "censorship" balanced adaptation. All the areas of the brain are represented in these structures. The "ego," in the sense of a tester of reality, is distributed, but a balanced adaptation to the various aspects of reality takes place in this million year old prefrontal addition to the brain of lower mammals.

I am convinced that the various psychometric tests can touch only the surface of this situation. They are too superficial to probe the mnemic possibilities of a million years of actual experience in nature.

I recall a story, once told here by Dr. Paton, of a student at Princeton who was found to have an intelligence quotient of 140 or so and was considered a genius. "Yes," said Dr. Paton, "he is an excellent case of dementia praecox."

Some of the complicated performance tests are of service in showing lacks in planned administration, or what Bianchi called the social sense. Some ethical-social inquiries arranged in psychometric form may go a bit further, but as most of these involve contemporary judgments, "none of which, like our watches, goes just alike, but each believes his own," they need scrutiny to establish anything approaching average norms for the eternal problem of truth and reality.

One may turn from structure and function and look at the loose generalization called "compulsion neurosis." Here, one is in the maelstrom of ideologic conceptions of a bewildering complexity. In terms of the general freudian formula, for not accepting which I see no good reason, the compulsion neurosis utilizes the mechanism of displacement arising from early erotic fixations and the displaced affect gains entry to consciousness by the substitution ritual mechanism, with much identification and distorting symbolization. Here there is much to support an argumentation that such complex syntheses are partly bound up in such a correlating switchboard as the prefrontal association areas. However, as the perception areas for different organ activities are widely separated in all parts of the brain and as some of these areas are more heavily loaded with libido investments than others, I question the general policy expressed by Charles Lamb's "roast pig formula" of burning down the house to roast a pig.

Psychoanalytic psychiatry has pointed to a highly important investment of organ libido in the "compulsion neuroses." This is the cathexis of the anal sadistic urge, with its massive hostility drives. The area for elaboration of anal sensory perception Dr. Penfield, I think, localized partly at the 1934 meeting.

If there is any sense in hobbling a horse to prevent his running away and if there can be isolation of the frontal association pathways of these areas for anal sensory perception, one might do some cutting instead of putting the whole instrument out of commission in order to correct a difficulty that possibly is localized in only a part of it.

Dr. Freeman speaks of the reduction in tension of affect. I doubt whether there can be any such reduction. Affect simply fails to be sublimated by higher degenitalized symbolizations and must find an outlet somewhere else. In other words, other organ systems must take over the energy investment. It is too early to say anything about this.

I cannot let the opportunity pass to speak of the desirability of accurate life histories in the sense outlined by Dr. Dollard. The history of the second patient reported by Dr. Freeman, whom I have seen, is highly dramatized; although there is no doubt as to the fact of the illness, let me cite from a letter by Dr. Meyer in answer to an inquiry of mine concerning the patient.

When Miss X was put on floor 1, that is, the floor of the disturbed patients, she dropped all her symptoms, to resume some of them on being removed to floor 2 or floor 3. In terms of Professor Hooton's apt title, "Apes, Morons and Men,"

when she was with the "apes" she was at home and had no need to exercise censorship. At her present state, she has probably simply been transferred to the moron class. As much of the actual work of the world has, in a sense, to be performed by the "moron" class, such an advantage may be debatable."

DR. L. E. HINSIE: Some of the major facts presented by Drs. Freeman and Watts may be stated as follows: 1. Characteristics common to the patients before operation. Each was an adult psychoneurotic invalid who had mental trouble for years before the operation. The emotions were severely invested in the morbid mental phenomena. Without treatment the outlook was unfavorable. 2. Characteristics common to the group after operation. Each achieved a measure of social improvement. The morbid mental phenomena were divested at times of the excessive emotions which they formerly possessed. Interests were gradually redirected to socially useful forms of activity. The intellectual status was not materially altered. There was lessening of emotional drive.

Thus, two clinical states are described for each patient. An intensely morbid psychoneurotic syndrome was followed by operation, and a less intense psychoneurotic syndrome resulted.

There is a distinct relationship, at least in time, between the operation and the alteration in the morbid condition. Whether there are other direct relationships cannot be determined at present. It is worth while, I believe, to carry the work further and to add data as a control to these preliminary observations.

It would be desirable to know whether the patient's illness had been reduced or ameliorated on previous occasions and, if so, to study the degree of improvement and the possible related factors. Was there any operation or injury prior to the one in question? What, if anything, happened to the morbid mental phenomena in connection with the operation or injury? One is often impressed with improvement in mental states that follows somatic injury.

The operation strikes directly at what the patient conceives to be the affected area. If it is gastrointestinal hypochondriasis, any direct medical or surgical procedure may occasion relief for varying periods. A psychoneurosis is "hypochondriasis" of the mind. The laity believe that the mind and the brain are one. Hence, any medical or surgical procedure that aims to remove a disability in the head may afford relief.

It is an open question, however, as to the factors connected with the relief from symptoms. It is probable that the operation has more profound influence on the psychologic than on the somatologic function of the patient. Patients with a psychoneurotic syndrome exhibit dysfunction with ideational and emotional features. Among the latter there are a strong sense of guilt and an impulse to injure. Dr. Freeman and Dr. Watts have undoubtedly taken such an important psychologic issue into consideration, although, since their work is empiric, they have not reported on the psychologic probabilities.

Their observations gain significance in that they represent important advances in the further understanding of the structure and function of the brain. Their findings may in a certain measure supplement those of Brickner. The history of surgical entrance into body cavities is replete with taboo. It is only within recent decades that abdominal surgeons have felt free from the criticism of the public and of their own colleagues. Thoracic surgeons are still under heavy restrictions; yet they are freer than cranial surgeons. In this day, therefore, the odds are overwhelmingly against experimental surgical treatment in relation to the cranial cavity and its contents. To explore the mind from a purely psychologic point of view is often regarded by one's colleagues as an unpardonable offense, although one may do nothing more than look.

I am less impressed with the clinical results reported for these patients than with the possibilities that the operative procedure may create in the field of clinical neurologic experimentation. I believe one will look forward with keen interest to furtherance of efforts along the lines suggested by this communication. Freeman and Watts have presented an operative procedure which to them may serve as a useful investigative instrument. Its relationship to the understanding and therapy of psychoneurotic syndromes is an open question.

DR. A. A. BRILL: Dr. Jelliffe and the others have so well evaluated this paper that I can speak only as a clinician. I cannot understand why such ideas are brought here, much less the fantastic conclusions drawn from them by some of the discussers. I suppose all are so polite that anything may be ventured with impunity. I know 2 of the 4 patients who furnished the material for the paper under discussion. One, Miss S., I have known for years, although I have seen her only once. When she first came to me, she showed a well developed compulsive neurosis, for which she had been treated at various institutions. She has kept in touch with me since, because I recommended sanatorium treatment. Lately she telephoned me: "Dr. Brill, I now feel worse than I ever did, and I will take your advice and go to the sanatorium." She added: "I am only sorry I did not write to you before I went to Washington. I had two operations and am worse than before."

The other patient, a report of whose case was not read by Dr. Freeman for lack of time, I have known for about eight years. He has had a number of attacks of manic-depressive psychosis, in which usually there was depression followed by euphoria. I have seen him only a few times, but during his first visit I told him what I tell every manic patient, namely, that he would get over this attack, treatment or no treatment, and that he should secure psychotherapy after the attack had subsided. He felt "fine" after a few talks with me, but he came back to me about a year later; I referred him to Dr. May Ginsburg for psychoanalysis. She soon reported to me that he felt "wonderful." I cannot see that there is anything in the history of these or the other patients to warrant the report of their improvement. None of them has behaved differently since the operation than patients with compulsive neurosis generally behave. The history of any patient with a compulsive neurosis will show ups and downs, which he usually attributes to some new treatment. Sometimes such changes come spontaneously. I reported such a "cure," which did not last long, at a meeting of the Massachusetts Psychiatric Society (*J. Nerv. & Ment. Dis.* **68**:561 [Dec.] 1928). During "recovery" the patient had not a single symptom of the numerous obsessions which assailed her for years.

Dr. Freeman admits that the patients still have compulsions but that their effect is dulled. I should like to know how he can measure the amount of effect. The presentation reminds me of the time when it was customary to treat homosexuality by prostatic massage. I recall a patient who had been so treated by a genitourinary specialist for two years, but he was still homosexual. The patient told me that he was willing to have prostatic massage, he liked it, but when the specialist began with instillations he refused to go on; he was then sent to me. Some time later, the same physician sent another patient to me whom he had treated for years by prostatic massage, without results. As the physician in question was a man of the highest type, I was sure that he must attribute virtue to such treatment; so I asked him how he expected to cure homosexuality by prostatic massage. He thought that the massage might rub out the "homosexual cells" and that they would be replaced by "heterosexual cells." I asked: "What are homosexual or heterosexual cells?" Being a witty man, he said: "You remind me of the woman who went to the bird store to buy a bird. She wanted a singer. The bird vendor said: 'Here is a male canary; male birds always sing.' 'But,' said the woman, 'he does not sing now; how do I know he is a male?' 'That's simple,' said the birdman, 'all you have to do is to throw him some worms; if he is a male, he will catch the female worms.' 'But,' retorted the lady, 'how do I know which is a male or which a female worm?' 'Well, Madam,' replied the bird vendor, 'I know nothing about worms; I am a birdman.'"

I tell this story to illustrate rather than to be funny. I believe that there is no reason that one should in any way be impressed by the seriousness of these presentations, in spite of the fact that I regard the authors highly. I know that they are seriously trying to contribute something to science, but what they showed is nothing but interesting experimentation. The material they presented this evening is no more conclusive of the validity of their claims than the putative cure of homosexuality by prostatic massage.

DR. H. A. RILEY: Has Dr. Freeman used this method in the treatment of agitated depressions?

DR. WALTER FREEMAN: In such a welter of ideas, I find my frontal lobes pretty well immersed and can answer only certain questions of the discussion.

Is this a radical operation? We think not. The frontal lobe comprises about 70 per cent of the cerebrum; we estimate that in the average case from 15 to 25 per cent of the frontal association fibers are transected. The best location for the cuts remains to be determined. We think we are getting closer to the ideal when we place them in the base of the frontal lobe, fairly far back and close to the midline. Cuts in this location, we believe, will most profoundly diminish the affect charge. Furthermore, the operation as done from above will be replaced by one done from the sides.

We do not believe that the results obtained here have been due to suggestion. Suggestion should be most effective when carried out at the time of first operation. In 2 of the cases reported substantial results came from the second operation. Postoperative psychotherapy in these cases has been minimal. We try to help the patients to get rid of their ideas, to help them to forget. Before operation they could not forget. We seek to aid that normal function of forgetting, which is apparently lost in persons with this neurosis.

How far does deterioration go? Is it compatible with a useful, active existence? I can think of a patient who is spontaneously recovering from an obsessive compulsive neurosis as her multiple sclerosis becomes worse, and I may call attention to the periventricular lesions of multiple sclerosis.

I have not seen dementia paralytica develop in a psychasthenic person, but I think that persons with early dementia paralytica who have been treated successfully with malaria maintain a fairly good standard of useful activity and possibly may be compared with those who have undergone prefrontal lobotomy.

Dr. Jelliffe's discussion touches the sublime, and no argument can detract from it. On the other hand, with Dr. Brill we cannot agree. The second case he spoke of was not the case reported in this paper.

To Dr. Riley I should say that 7 of 10 patients with agitated depression are substantially relieved.

As to operations performed on other parts of the body in the hope of curing delusions: I may quote a sentence from Da Costa (Da Costa, J. C., in Keen, W. W.: Surgery; Its Principles and Practice, Philadelphia, W. B. Saunders Co., 1907, vol. 2, p. 811): "All such attempts partake of the sort of wisdom which would lead one to tinker a weather-vane in hope of altering the wind, or to attack a thermometer in order to regulate the temperature."

Our motto has been: "If the trouble is in the brain, why work on the belly?"

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

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SURGICAL THERAPY FOR CERTAIN CONVULSIVE DISORDERS. DR. IRA COHEN.

Convulsions in cases in which operation is indicated are, according to Penfield (Epilepsy and Surgical Therapy, ARCH. NEUROL. & PSYCHIAT. **36**:449 [Sept.] 1936), usually associated with tumor, cerebral cicatrix from various causes, focal atrophy or subdural exudate. With Geyelin, Penfield reported a remarkable group of 5 cases of familial epilepsy (Cerebral Calcification Epilepsy, ARCH.

NEUROL. & PSYCHIAT. **21**:1020 [May] 1929). In operations on patients with focal convulsions, my associates and I have encountered 5 instances in which the etiologic factor did not fit into any of the aforementioned categories. In 2 cases calcification was the inciting agent; in the other 3 the convulsions were local manifestations of a disseminated process.

The first case was that of a married woman aged 29 who at the age of 18 had one hundred and thirty convulsions in a period of three days. These were followed by right hemiplegia and aphasia, from which she recovered completely in a month. After an interval of seven years without convulsions, she began to suffer from momentary attacks of mental blankness, at times associated with writhing movements of the upper extremities. She was admitted to the hospital after four days of severe headache and mental confusion. She had partial aphasia. Several convulsions were noted on the right side. On the third day of observation she lapsed into deep stupor, and an exploratory craniotomy was carried out on the left side for suspected tumor. In the parietal region a multilocular cyst containing clear fluid was opened, and a calcified plaque 1 cm. in diameter was removed. The wall of the cyst showed reactive gliosis. In the eighteen months since operation there have been four minor seizures of a few seconds' duration.

The second case was that of a man aged 32 who had had generalized convulsions for eight years. The attacks were becoming more frequent. The only physical findings were slight weakness on the right side of the face of central type and right homonymous hemianopia. Roentgen examination showed three calcified areas in the left occipital lobe. The diagnosis was possible tumor, and exploration was carried out. Two of the calculi were removed. There was neither gross nor microscopic evidence of tumor. Ossification was observed in the calcified masses. The convulsions continued after discharge, and the patient was returned to the hospital eight months later for removal of the remaining calculus. At the second operation it was necessary to amputate the occipital lobe. In the two years since there have been no general convulsions. In the first year there were three momentary attacks of mental blankness.

In neither of these 2 cases was the etiology of the calcification clear. In fact, the character of the calcific lesion seemed different in the two cases. In the first case there were a thin plaque and scattered calcium in the walls of the blood vessels; in the second case massive calculi with formation of bone were removed.

The third case was that of a child aged 2 who began to have convulsions at the age of 3 months. Up to two weeks prior to admission to the hospital, the convulsions were generalized. They then became jacksonian in character, involving the left side. The child had weakness on the left side and a calcified plaque in the right frontal area. At operation a nodular mass in the prefrontal area was exposed and removed. The diagnosis was tuberous sclerosis. For two years the patient was well; during the third year she had one seizure. During the first half of the fourth year the attacks were more frequent; since, they have been occasional.

The fourth patient first came under observation at the age of 11 years. The convulsions began at the age of 16 months and were of jacksonian type up to the age of 5 years, after which they were generalized. Examination revealed pseudoathetoid movements of the left arm and left hemiparesis. Exploration showed several nodular masses. Biopsy of one was reported to indicate tuberous sclerosis. Nothing further was done until three years later. Because of continued convulsions a second operation was performed, and by electrical stimulation the supposed epileptogenic area was identified and excised. There have been no convulsions in the eighteen months since operation, but there have been almost daily sensory fits.

In the 2 cases of tuberous sclerosis the diagnosis was made before excision of the cortex, and it was realized that the excised tissue represented only part of a more generalized process. The excision was carried out in the hope that the convulsions might be influenced. In both cases this symptom was ameliorated. A different type of lesion, but an even better result, is reported in the next case.

Case 5 was that of a youth aged 20 whose seizures began four months prior to his admission to the hospital. They were of jacksonian type, involving the right side and the arm more than the leg. He had up to sixteen attacks a day. He was euphoric. There were signs of disseminated disease. The patient was left handed. At operation the epileptogenic area was identified by electrical stimulation and was excised. Since operation three years ago, there has developed a classic picture of multiple sclerosis. The patient has not, however, had any seizure since his discharge from the hospital.

Cases in which a non-neoplastic calcified area was removed have not been reported as often as one would expect. When the lesion is associated with convulsive seizures it may be the epileptogenic focus, and removal may be of benefit.

The presence of a disseminated lesion does not in itself contraindicate local cortical excision for amelioration of focal convulsions.

DISCUSSION

Dr. Charles Elsberg: This isolated group of 5 cases provides little matter for discussion. Certainly, this is neither the time nor the place to enter into a discussion of what are the causes of convulsive seizures from localized, non-neoplastic lesions in the brain or whether the disease, if it can be called a localized disease, is not from the beginning diffuse, perhaps with concentration of the pathologic change in one part of the brain. To hear a report of a series of cases of this kind, in which, as the results show, the operations have been performed with great skill, reminds me of the conditions that obtained twenty or thirty years ago, except that the pathologic studies are much better now. At that time one tried to operate on all patients who had more or less localized convulsive seizures attributable to a lesion in a localized part of the brain. Every once in a while there was an astounding result, not only because the patient usually received a great deal more therapy after than before the operation but because of the operative procedure itself, so that the seizures either ceased altogether or were changed in character for a number of years, and perhaps for the rest of the patient's life. In the majority of instances, however, a year or two passed during which there was either marked diminution in the number of attacks or disappearance of the attacks; then gradually, in spite of everything that had been done, there was recurrence of the symptoms, which ran the usual course in a case of convulsive seizures. I suspect that in the 2 cases of tuberous sclerosis this will be the course, and I am sure that Dr. Cohen thinks the same. At present one is forced to operate on a certain number of patients with convulsions. Occasionally one thinks that there is a neoplasm and no neoplasm is found. At other times operation is performed because of localized seizures, with no thought of the presence of a neoplasm. I venture to say, however, that the time is coming when a large number of these patients will be treated by some other method. Through electroencephalography, convulsive seizures will be subdivided. One will find that if one can excise the affected part, the part that leads to the motor cortex, one may accomplish a great deal more than by operating on the motor cortex; it may be found, on the other hand, that the procedure must involve the motor cortex. I therefore feel that the last word has by no means been said. One must be conservative in expecting results in cases of this kind. Certainly, in the cases described by Dr. Cohen there are evidences of skilful, and possibly successful, surgical treatment, but the last word with regard to convulsions not due to neoplasm, or even to conditions associated with calcified plaques or cerebral calculi, has by no means been said.

Dr. Joseph H. Globus: In commenting on this paper I may add some observations and then offer an interpretation. The questions arise: What is the origin of the calcium, and what is the significance of its presence? It is my belief that the deposits of calcium have origin in what I call mummified blood vessels. I base this statement on an observation in connection with tumors of the meningeal variety. There I often observe that vessels which enter the tumor are cut off from the source of supply. Such vessels do not participate in the circulation of the blood and hence become physiologically dead. Dying or dead blood vessels undergo calcification. The blood within the vessels becomes stagnant and under-

goes disintegration, and calcium is again liberated. The history of the so-called psammoma bodies in meningiomas is, in my opinion, similar to that of the mummified blood vessels; the calcium deposits have a similar origin. They are little else than landmarks or tombstones of dying or dead (mummified) blood vessels.

Another question is: What is the relation of these deposits of calcium to the clinical picture? Are the deposits responsible for the convulsive seizures? It is possible that they are provocative of epileptiform attacks, but it is more likely that they represent landmarks of some other pathologic process which is productive of the convulsive seizures. In 2 instances it was possible to establish the existence of nodules characteristic of tuberous sclerosis. This is also a disease in which deposits of calcium are prominent in the nodules. Here again, the calcium deposits are due to dying or dead blood vessels. It was possible to recognize the deposits in these 2 instances as part of the picture of tuberous sclerosis, and it is not at all unlikely that in the other 2 cases tuberous sclerosis was the true pathologic process, although it was not disclosed by the meager histologic material. Hence, in 4 of the 5 cases, one may assume that there was a disease process either typical of or akin to tuberous sclerosis; if one agrees that tuberous sclerosis is the disease process in 4 of the 5 cases, how can one explain the convulsive seizures, a condition which is prevalent in cases of tuberous sclerosis? Here I permit myself to speculate. I have noticed that in tumors associated with tuberous sclerosis there are extremely large nerve cells with very long processes that make connections throughout distant parts of the brain. These cells have retained many potencies of the unripe cell; they, therefore, can be more readily provoked into activity. By their extremely long processes they may convey an impulse to motor cells which are responsible for the explosive motor discharges. Dr. Elsberg had that in mind when he spoke of lesions elsewhere in the brain capable of stimulating cells within the motor area of the brain. I believe, then, that in 4 of the 5 cases the calcification was nothing more than an indication of another pathologic process, probably of blastomatous character, such as tuberous sclerosis.

Dr. Israel Strauss: It is true that one is seeking to alleviate a condition called epilepsy, in which one finds clinical evidence of a focal lesion. One is almost forced, because of ignorance of the nature of the lesion, to examine the brain and ascertain what is there. In the 2 cases of calcification reported, no evidence of disease of the brain was found other than the hemianopia caused by the calcified bodies. One could tell nothing regarding their nature until they were removed; even then, the pathologist, Dr. Globus, was not certain of their origin, although he has offered a good speculative idea. I wonder about his assertion that the blood vessels in the lesion are dead vessels. If I am not mistaken, one of them showed bone formation. That is difficult to associate with a dead blood vessel. After all, the lesion being of uncertain origin, as even Dr. Globus said in his report, what is the clinician to do in the face of such a focal clinical picture except to resort to surgical means for removal of what may be an offending body in the brain, ignorant of its nature though he may be? Take, for instance, the 2 cases in which the disease later proved to be tuberous sclerosis. There are cases of tuberous sclerosis in which the disease is recognizable clinically. On the other hand, there are cases in which the disease is not so recognizable, although it may be suspected. If the day comes when one can recognize, either by electroencephalography or by some other method, the nature of this unusual and interesting pathologic process, one will not subject a patient to operation, for one will recognize, as Dr. Elsberg has stated, that in the face of such disease one cannot hope for a cure. Only temporary relief may be obtained, as Dr. Cohen suggests. I should make only this criticism of Dr. Cohen's method, though I am not certain I am right: He removed the rolandic area, but some cells in the prefrontal area were spared. It might have been worth while to go further and produce more permanent paralysis. That is speculative. Undoubtedly there would have been greater damage to function if that had been done, but if a recurrence of the epileptic state had been prevented, it would have been well worth while to

substitute paralysis for convulsions. I question whether that operation would have been any more successful than the procedure reported; so it seems to me that Dr. Cohen accomplished his object. In the case of multiple sclerosis, even though amelioration of the convulsive seizures did occur, I do not know but that Dr. Cohen, if he had known the nature of the disease, would have said "Let well enough alone!"

DR. JOSEPH H. GLOBUS: Dr. Strauss's objection that bone formation is not in accord with the suggestion I made regarding the origin of calcification may be met by the fact that deposits of calcium are notorious for their tendency to duplicate the structure of bone. That does not mean that it is true bone. When one sees it under the microscope, one describes it as bone, but one does not assume that it is really bone.

The other matter to which I wish to call attention is this: One speaks of tuberous sclerosis as a diffuse disease. I should speak of it rather as a disseminated disease. I have seen instances of tuberous sclerosis in which the nodules were few and isolated. Recently, I reported 2 such cases in which there were two minute nodules and no evidence of tuberous sclerosis elsewhere in the brain. When one realizes that there occur instances of tuberous sclerosis in which small nodules are limited to one part of the brain, if one can identify their location, extirpation is unquestionably indicated.

DR. IRA COHEN: In the third case reported I voluntarily performed the second operation, even though I knew the diagnosis from a biopsy specimen taken at the first operation; I believed that, in spite of the fact that the disease was diffuse, one might relieve the distressing symptoms by removal of the nodule. Operation gave relief for two years.

I agree with Dr. Elsberg that one does consider operation for cure of convulsive seizures in a case of disseminated disease. The cortical excision was not made in the motor area in every instance. In some cases it was well postrolandic. It is because of the striking result in some of the cases in which the convulsions were relieved or their character was changed that I thought it worth while to report this series to the society.

EPHEDRINE IN TREATMENT OF PETIT MAL CONVULSIVE SEIZURES OF AUTONOMIC ORIGIN. DR. I. S. WECHSLER.

While it is well known that seizures often show features which betray their subcortical origin, it is not generally recognized that some reflect dysfunction of the hypothalamic vegetative centers. The following 2 cases illustrate such dysfunction and the favorable therapeutic response to ephedrine sulfate (a drug which seems to affect the interbrain) after failure of treatment with bromides and phenobarbital.

Case 1 is that of a middle-aged woman who after a fracture of the skull experienced infrequent major convulsions and innumerable daily petit mal seizures which did not respond to any treatment. The latter attacks were characterized by a feeling of apprehension, generalized weakness, fleeting loss of orientation, as if things were disappearing under her, marked pallor and palpitation. The pulse rate rose from 80 to as high as 150 per minute, and the systolic blood pressure sank to 90 mm. of mercury. The spells lasted for from a few seconds to several minutes and were never accompanied by loss of consciousness. They practically incapacitated the patient. Because of the autonomic features, ephedrine sulfate in doses of ⅜ grain (0.024 Gm.) was prescribed twice daily. The seizures ceased promptly.

Case 2 is that of a woman aged 24 who, in addition to major convulsions which occurred mainly at night, had many diurnal and nocturnal attacks unattended by loss of consciousness. These were characterized by sudden onset of rigidity, extreme waxy pallor, rise in pulse rate and fall in blood pressure. The peculiar rigidity consisted in extension of the arms and legs and bending of the body

almost into a U-shaped figure. These exhausting seizures occurred mainly when the patient lay down and tried to relax. As other treatment failed, ephedrine sulfate was given orally. Gradually the seizures diminished and for a time ceased altogether. After several months of treatment, she still has an attack occasionally. The major fits have not been affected by the ephedrine. Nonetheless, from being totally incapacitated so that she was compelled to give up her position, she has become sufficiently well to resume her occupation. Although no etiologic factor could be determined in this case and neurologic examination gave normal results, it is possible that what passed for severe influenza, which occurred six months before onset of the seizures, may have been unrecognized encephalitis.

These 2 cases have some resemblance to that described by Penfield (Diencephalic Autonomic Epilepsy, ARCH. NEUROL. & PSYCHIAT. **22**:358 [Aug.] 1929), but they are dissimilar in many respects. Whereas in the case of tumor which Penfield described there were flushing and initial rise of blood pressure, in my cases there were pallor and fall in pressure. Perspiration and salivation were absent in my cases. In all there were rise in pulse rate and preservation of consciousness. The seizures in Penfield's case terminated in hiccup, a feature lacking in the present cases. Despite the dissimilarities, there were enough features in common to justify interpretation of the seizures as autonomic and to attribute them to dysfunction of the hypothalamus. The prompt and favorable response of the attacks to ephedrine, after failure to respond to bromides, which are so effective in treatment of cortical petit mal seizures, is further proof of their diencephalic origin. That they belonged to the convulsive state may be inferred from their paroxysmal nature and their association with convulsions. The lesson to be drawn is that some petit mal attacks may be of autonomic origin and that meticulous observation and correct interpretation of the special features may lead to differentiation of this small subgroup from the larger group of the convulsive state.

DISCUSSION

DR. FOSTER KENNEDY: The cases reported by Dr. Wechsler are, I think, of enormous importance. They serve to point out that epilepsy is a protean phenomenon, the character of which is determined largely by the site of the explosion. As Dr. Friedman just said to me, the attacks described by Dr. Wechsler might well have been described by Gowers as vasovagal attacks—sympathetic and parasympathetic storms. Such is the character of convulsive attacks appearing after encephalitis has affected the midbrain. I remember a case of postencephalitis in which there were an enormous number of attacks of this kind nearly every day. The patient described her consciousness as becoming remote, like a very small light high in the apse of a high cathedral. She was aware that she was conscious, but she had to hang on to consciousness to be aware of it. In true epilepsy one need not postulate unconsciousness as a *sine qua non*. An alteration in the stream of consciousness is sufficient, and sometimes in true epileptic seizures consciousness is subjectively extended, as in certain attacks of temporosphenoid origin. For that matter, what before I have called the spectrum of epilepsy, in which one kind of attack blends into another as the colors in the spectrum blend into one another, may be considered to include even certain phenomena which are called hysterical. There is made almost too sharp a line between epilepsy and hysteria. I am not sure that the term hysteroepilepsy is often not better. It was abandoned with scorn by my generation, but I think that it ought to be used again because the peculiar analogy between certain motor phenomena appearing in hysteria and motor phenomena produced by structural change in the midbrain cannot help but force itself on one's attention. The carpopedal spasms, the peculiar striatal-like movement of compulsive hysteria, must mean that the personality—whatever that may be—retreats and ceases to use the ordinary neopallidal mechanism, but employs the mechanism of a phylogenetically older type. The hysterical patient with striatal and hypothalamic phenomena is often a perfect mimic. Dr. Angus Frantz today

suggested to me that the disease may sometimes respond well to ephedrine because it is "allergic epilepsy," but probably both Frantz and I are "hipped" on that subject!

DR. S. BERNARD WORTIS: There is another aspect of the problem which perhaps requires emphasis. In 1 of Dr. Wechsler's cases there was low blood pressure. In the other a change in the menstrual cycle followed trauma. Has Dr. Wechsler considered the effect of impulses arising in the carotid sinus as the possible causative factor of the convulsions in both his cases? I bring this to attention because most persons subject to convulsions are rarely tested for hypersensitivity of the carotid sinus. Early experimental observations of Pagano (1900), Sollman (1912), Koch (1923) and Heymans, Weiss and others have shown that impulses arising in the carotid sinus and carotid body can effect changes in the heart rate, blood pressure and function of the brain. Earlier clinical reports related the effect of simple pressure on the carotid artery to impairment in the cerebral blood flow or to the action of the vagus nerve in slowing the heart, with resultant syncope. More recent work seems to indicate that the effects obtained (syncope, convulsions and related states of impaired consciousness) are really caused by stimulation of the carotid body.

Weiss and his co-workers have aptly subdivided the clinical effects of stimulation of the carotid sinus into three groups: 1. The cerebral type of reaction, in which mechanical stimulation of the carotid sinus results in alterations of consciousness (dizziness, syncope, amnesia, narcolepsy, cataplexy and convulsions) with no preceding slowing of the heart rate and no preceding fall in the systemic blood pressure. This response to stimulation of the carotid sinus is not helped by medication with atropine or epinephrine, but is enhanced by digitalis and sodium cyanide. In cases of stubborn type it may be necessary to denervate the carotid body to prevent recurrence of these attacks.

2. The vagal type of reaction, in which stimulation of the carotid sinus produces cardiac asystole with resultant cerebral anoxemia and alterations of consciousness. This reaction is helped by atropine (which abolishes the vagus effect), epinephrine and ephedrine (which raises the systemic blood pressure). This syndrome is enhanced by digitalis or acetylbetamethylcholine.

3. The depressor type of reaction, which is the least common and is characterized by fall in blood pressure and cerebral anoxemia with the changes in consciousness common to the other types of response. Such patients are helped by epinephrine and ephedrine but are made worse by nitrites because of the respective effect of these drugs in raising or lowering the systemic blood pressure.

One should look for local abnormalities in the region of the carotid sinus, such as inflammatory disease, tumors, enlargement of glands and sclerotic arteries. Furthermore, systemic disease, such as syphilis and avitaminosis, and the menopause are known to contribute to hypersensitivity of the carotid sinus, and suitable therapy should be tried before resorting to denervation of the carotid sinus.

I mention these syndromes because I wish to know whether Dr. Wechsler tested his patients for hypersensitivity of the carotid sinus. It seems that syndromes such as he describes might arise from this source.

DR. E. D. FRIEDMAN: I think that all agree that the grouping of symptoms which is called epilepsy is, as Dr. Kennedy has said, a spectrum of syndromes. Most are in accord also with the notion of the older school that the onset of the epileptic fit in many cases is characterized first by tonic spasm, which means recession of the organism to the level of the overtoning mechanism of the midbrain, and then, as the patient returns from this lower level, by a clonic phase, due to return of cortical function. When the organism descends to the midbrain level it becomes a more or less vegetative mechanism and shows evidence of disturbed autonomic balance. Some may remember a book by Frisch, of Vienna, entitled "The Vegetative Nervous System in Epilepsy," in which he undertook to prove that there is a disturbance in the autonomic nervous system of all persons with epilepsy. This predisposes to epilepsy and lends support to the view of the

older authors who spoke of an "epileptic constitution"—something in the patient which makes him prone to the disturbances which are called epilepsy, whether these are of minor or of major form. A number of years ago I reported at a meeting of this section (Epilepsy with Coincident Vagotonic Crises, ARCH. NEUROL. & PSYCHIAT. **24**:1094 [Nov.] 1930) a group of cases in which, either during or immediately after the seizures there developed pronounced evidence of vagotonia in the form of small pupils, salivation, perspiration, bradycardia or marked arrhythmia of the pulse and severe constipation.

Dr. Wechsler's cases add additional evidence of the fact that one is dealing with such disturbances of the vegetative nervous system in cases of epilepsy.

DR. ISRAEL STRAUSS: I wish to give a word of warning to those who will use low blood pressure as a symptom pointing to involvement of the hypothalamus in so-called epilepsy. They will err greatly. I have noted that in every case of so-called idiopathic epilepsy there is a low blood pressure. I have noted it so often that before I take the blood pressure I predict what it will be; I have often wondered why it is so universal and what is the cause; I have never satisfied myself as to the explanation or heard any one stress that feature and its universality.

Of course, when one discusses the carotid sinus syndrome one is not dealing with the result of a blow on the head and a hemorrhage, such as were present in Dr. Wechsler's case. I have been fortunate enough to see and diagnose oversensitivity of the carotid sinus in 1 case. The patient was referred to me by Dr. Edward Stern, who suspected the effects of pressure on the carotid sinus, at least in the neighborhood of it. The patient was referred to Dr. Soma Weiss, was operated on and is well. The case will be reported. The symptomatology exhibited in this case was not in any respect similar to that in Dr. Wechsler's cases. Dr. Wechsler suspects that there is involvement of the hypothalamic region in his 2 cases. Thus far, he has had success with the drug in these cases, but I venture to say that in other cases of what is thought to be epilepsy ephedrine will be tried, with no result. I am not sure whether Dr. Wechsler will agree with me; the point, however, is that in cases of frequent petit mal attacks of this type he found that there were certain symptoms, call them vegetative, which seemed to have started in the hypothalamic region; the giving of a drug which seems to have influence on that region of the brain did something in these cases. That is worth remembering and trying, but it does not mean, as Dr. Wechsler will agree, that epilepsy will be relieved by ephedrine. There is a condition which might be relieved by this drug. I suppose all have seen cases of repeated attacks in children in which no drug had any effect. I have made encephalograms in these cases and have even tried the ketogenic diet in 1 instance, with no result. The condition as a rule ends in recovery; I wonder whether the one thing I have forgotten is ephedrine.

DR. GEORGE H. HYSLOP: I wish to make a few comments on Dr. Wortis' remarks about the carotid sinus syndrome. The subject is relatively new, and perhaps its novelty gives it a special appeal. Dr. Wortis suggested that one should examine the neck carefully for the various lesions which may affect the carotid sinus.

I have seen at least 250 patients at the Memorial Hospital with demonstrable pathologic lesions in the region of the carotid sinus, and I have yet to see one who has had epileptiform or other paroxysmal phenomena.

DR. ISRAEL S. WECHSLER: I agree with what Dr. Kennedy has said; so I have nothing to add to his remarks.

To answer Dr. Wortis: Frankly, I did not think of the carotid sinus syndrome in this connection. In the first case I saw the patient once and have directed treatment by mail since. In the second case I did not think of trying pressure on the carotid artery, but I shall the next time the patient comes to see me. Dr. Friedman's remarks are pertinent, and I am grateful to Dr. Strauss for his discussion.

My reason for making this presentation is not so much its inherent clinical value—that seizures which failed to respond to every other treatment yielded to

ephedrine—but the need to think of clinical phenomena in terms of anatomy, pathology and physiology. There is still opportunity for the clinician to make meticulous observations on the various cerebral manifestations which he commonly encounters. One is too apt to accept statements at their face value just because they are made repeatedly. For example, Dr. Friedman said that the fit invariably shows first a tonic and then a clonic phase. I am not sure that is true in all cases. There are infinite varieties of the petit mal attacks, and they must have significance. It seems worth while to analyze the various aspects and their sequence, grouping and relationship to other phenomena. One may then dissociate small groups from the larger group of convulsive states. It may also enable one to revaluate symptoms which have hitherto been explained in a glib, but perhaps not correct, way. It will be recalled that some time ago I presented before this society a review of seizures which occurred only in certain postures, namely, when the patient lay on one side, was going to sleep or was arising.

One may take, for instance, two well known symptoms: the epileptic cry and the sudden loss of urine, or incontinence, during the fit. The cry is explained by a sudden spasm of the larynx and the escaping blast of air which results in a sound called the cry. It seems to me that that is not true. The epileptic cry is not a hoarse or shrill sound, as if a blast of air were passing through a narrow aperture; it is a weird cry. It is easily recognizable; it ushers in the fit and may come even before the patient falls and becomes rigid. Penfield elicited exactly the same type of cry on stimulation of the cortex during the course of operations on patients who were conscious; they did not know they had cried out until after the cry came forth. Perhaps the cry has localizing value. In any case, not all patients emit cries; in fact, most do not. Whether the cry points to the source of the epileptic discharge or is an episode in its course is a matter for discussion.

Micturition takes place suddenly in the first stage of the fit. It may occur between the first and the second stage, the first stage lasting from thirty seconds to a minute; usually it is one of the earliest phenomena. I wonder whether micturition is not also a sign of localizing value. One knows that the paracentral lobule has something to do with urination. Patients with a parasagittal tumor may have paraplegia and incontinence. The loss of urine is not due to loss of consciousness; it is the result of impairment of function. I have seen patients with tumor of the midbrain and interbrain who had disturbances of urination, either of retention or of incontinence. Therefore, it seems to me that incontinence during the fit must be evaluated in terms of localization. Otherwise the question arises: Why does not every patient who becomes unconscious during a fit have incontinence of urine? It should be emphasized that only a few do.

To repeat: Clinical evaluation of the little signs may lead to physiologic and anatomic correlation. Meticulous observation of the "little," and often overlooked or unrecognized, phenomena may lead to the justifiable conclusion that there are no silent areas in the brain. I once said facetiously that the brain has no silent areas but that one is silent because one does not know all its functions. When one comes to know the physiologic, anatomic and pharmacologic meaning of the "little" phenomena, one will become more articulate clinically, and so will the brain. It is for this reason that I believe that observation of the autonomic phases of certain petit mal attacks and their correlation with the vegetative brain "centers" have some value.

PERVERSE TENDENCIES AND FANTASIES: THEIR INFLUENCE ON PERSONALITY. DR. SANDOR LORAND.

Four cases in which there was treatment by psychoanalysis are reported to illustrate how character traits and peculiarities of personality may result from repressed perverse impulses and fantasies. Outstanding in all these cases was the fact that the patients presented no overt neurotic symptoms. They were unhappy and unable to find a place in the world, suffered from feelings of inferiority

and spent the greater part of their time day dreaming rather than acting. On closer investigation all these traits proved to be late manifestations of infantile erotic tendencies carried over from childhood.

The general dissatisfaction with life was closely connected with inability to experience pleasure, especially in the sexual sphere; the inability itself was due to a continuous struggle with the remnants of bisexual tendencies, both psychologic and physiologic. Women of this type grow aggressive as a result of the pressure of their masculine drives and have difficulty in accepting the feminine role, although they may seem entirely feminine. Men of this type spend their energies denying and concealing their feminine trends and worrying about the impression they make on others. Both men and women fail in their sex relations with each other, and often in their social relations and work as well. The unconscious homosexuality distorts their actions in and their relations to their environment. Since the sublimation of the asocial erotic drives is only partly successful, the emotional life is constantly disturbed.

Persons of this type derive gratification from various infantile practices, such as masturbation and sadistic and masochistic fantasies. They have strong exhibitionistic and voyeur drives, which they must repress; they live in dread of revealing any of these trends, even to a degree that would be considered normal. The pressure of these repressed unconscious impulses inhibits the development of a strong ego; it follows, then, that they are unsuccessful in what I should call the normal sublimation of erotic drives.

The therapy of such patients presents initial difficulties because they seem so unemotional. This attitude, however, is soon recognizable as the defense against feeling emotion, and as such must be broken through. The habit of intellectualizing must be replaced by an awareness of the emotional reactions. By this means reorganization of the emotional sphere may be effected.

DISCUSSION

DR. A. A. BRILL: As I listened to the learned discussion of the first two papers and then to Dr. Lorand's paper, I said to myself: "Happy are my friends the neurologists, who do not have to discuss everything below the waistline and can confine themselves to decent, respectable things!" When Dr. Lorand tries to give the results of about four years' work in half an hour, one cannot be expected to follow him as one did Dr. Wechsler, who saw one of his patients in the interval between consultations with two other patients and continued to treat the first patient by correspondence. I have been doing psychoanalysis for over thirty years, and I never had the courage to come before an audience like this and attempt to do what Dr. Lorand tried to do this evening. I think that he undertook too much, and I doubt whether he carried over his points. What he wanted to convey was Freud's conception of normal sexuality and its course in the neuroses and the perversions. Freud maintains that unless a person reaches the genital level and finds an object he is not normal. He claims that the child's sexuality is disseminated. The child can secure gratification from various parts of the body, which to an adult would be abnormal. The child is gratified by touching, looking, tasting and smelling; then, because of training, he gives up these primitive impulses; he represses and sublimates them in part and subjugates the rest to the primacy of the genitals. If these various phases proceed normally and a person reaches puberty and looks for a normal heterosexual object, he has no neurosis. If anything happens to prevent or impede that development, weak spots of "fixations" may result; any one of these primitive components may persist into adult life and show itself as a perverse tendency or as a perversion; on the other hand, it may change into its negative, and the patient may have a neurosis. That is what Dr. Lorand was trying to say when he gave the results of his workmanship in these 4 fascinating cases. I wish one could read the analyses in all the cases as he worked them out; one could spend many hours on each case. I am convinced that Dr. Lorand did not bring out all the points in the cases he reported—that would be impossible in so short a time.

He concludes that some persons of this type cannot possibly be properly adjusted because there is something inherently unstable in them. He thinks it may be of a physical nature. One cannot do everything, but Dr. Lorand learned a great deal from these cases. I learned a great deal from reading his paper, but I realize that he did not convey everything tonight. He would have done better if he had reported one case and had dilated on it. He could have shown the various steps in his analysis, which led from the abnormal, perverse tendencies to normal adjustment. Nevertheless, I think that Dr. Lorand has done one vital thing. All may not have been able to follow him, but I noticed that some of the subjects he mentioned were stimulating and some shocking; long experience has taught me that when people are stimulated or shocked by anything they usually become curious and try to find out more about the subject; this was really the object of his paper.

DR. ISRAEL STRAUSS: I wonder why Dr. Lorand asked me to discuss his paper. I read it and was fascinated, but I admit that I do not understand phases of it. He begins by saying that biologically people are bisexual. I have heard a great many psychiatrists make statements like that, then continue with the rest of the paper and forget all about the bisexuality except as it expresses itself in the unconscious. At a certain stage of embryonic development, no means is known by which the sexes can be differentiated.

In the adult male or female there are vestiges of the sexual apparatus of the opposite sex. In the growth of the young adult, activities of the endocrine system may cause individual persons to show bodily changes which point to secondary characteristics of the opposite sex. In the Westchester Division of the New York Hospital, Henry studied a number of homosexual women who showed a bodily structure many features of which were characteristic of the male sex. Therefore, in appraising the perverse tendency of the human organism it seems to me that the psychiatrist should attempt to evaluate the role played by physical characteristics of the organism in development of the personality.

I do not know whether Dr. Lorand in his study of the unconscious in these cases made any note of the physical makeup of the patient. It might be an interesting field for research if the psychoanalyst would make an intensive study of the types that I have mentioned.

DR. C. P. OBERNDORF: I hoped Dr. Lorand might tell how perverse tendencies and fantasies influence personality. I think that is the title of his paper. I did not hear an accurate definition of personality, nor could I grasp how the fantasies in his cases had influenced the formation of personality. For that reason, it seems to me that Dr. Lorand has reiterated the early psychoanalytic concepts concerning conflicts between homosexual and heterosexual tendencies. Such conflicts appear in practically every analysis. The subject is in some way confused and undecided as to which pattern of conduct he should follow. One finds that memories of homosexual longings are often deeply buried, exert their influence quite unknown to the subject and affect his actions and his character formation. For instance, some of the most feminine women use their femininity as a cloak for unconscious homosexual fantasies, which in turn cause pathologic manifestations ranging all the way from uneasiness in the company of women to serious forms of mental disintegration, such as compulsions and paranoid formations.

That there may be a biologic background does not alter the validity of psychologic explanations. Freud himself was one of the first to see that back of such conflicts there may be a biologic or physiologic reason. I recall distinctly bringing up this question with him in 1922. As I remember it, his reply at that time was: "Let the endocrinologists, the biologists and the physiologists go as far as they can in their investigations. We will go as far as we can in ours. Some day the opposite approaches will meet." At present, the investigations with hormonic substances conducted in laboratories all over the world indicate that it soon will be at least partially determined what makes a certain person more susceptible than another to similar psychologic impressions. Probably within the

next ten or twenty years psychoanalysts will not work alone with psychologic influences causing mental symptoms but will enlist the help of biochemists and biopsychiatrists in aiding neurotic and psychotic patients to recover more rapidly by methods unavailable today.

DR. SANDOR LORAND: I have nothing to add but to thank Dr. Brill for his gracious remarks and his elaboration of the problem presented. As regards the question of cure: One of the patients, the absent-minded woman, was cured, and lives in the West with her children, quite happily, to the best of my knowledge.

Another case is that of the furrier. I did not see him for nine years. Last year we met in a club, and he introduced me to his wife. They have three children. As I told you, he was impotent when he consulted me. He is now happily adjusted. Another patient with impotentia is still under treatment, an intelligent young man with a career before him, and I hope to cure him.

In reply to Dr. Strauss's statement that nothing is known of the causes of a weak ego: I should say that, on the contrary, much is known. For example, even when two persons have slept with their mother the circumstances may not have been quite the same. I had a patient who, as a child of 1½ years, had suffered from a renal trouble for about a year. He slept with his mother at the time. He knew later only what the family told him about his early illness. His brother also slept with the mother. The brother was healthy; the patient became obsessed later in life, as a result of his sexual difficulties, with the idea of constantly urinating. It is true, he may have had a weak constitution, but his emotional attachment to his mother was what made the difference between his weak ego and his brother's normal ego. He became quantitatively more strongly attached to the mother than the brother did. One may therefore be justified in considering the quantitative differences in emotional experiences as responsible for neurotic difficulties. The proof is that one is able to cure the patients, build up their egos and reorganize their personalities. If the weak ego were a purely constitutional matter, one could not change it psychologically.

What Dr. Oberndorf said as to my presenting nothing new is true. However, this paper was given not to psychoanalysts but to neurologists and colleagues. It is true that all neurologists are psychoanalysts to some extent: all use dream interpretation, speak of the unconscious and employ some freudian terminology. It was Freud who had to show the significance of these things.

I presented this paper to teach something of the problems with which one is confronted in treating certain types of neuroses to those who are interested in tackling these problems, even by methods that are not purely psychoanalytic. My aim was to present certain problems by means of which it would be possible to grasp the significance of bisexuality, both organic and psychologic. Returning to Dr. Strauss's remarks on cure: One must be elastic in interpretation in that respect. I never think that I have effected a 100 per cent cure. I do not expect any one here to do that. If I make a 75, or even a 50, per cent cure, I am satisfied. If I make a person 40 per cent happier I am content.

Book Reviews

The Etiology of Mental Deficiency with Special Reference to Its Occurrence in Twins. Psychological Monographs, vol. 48, no. 4. By Aaron J. Rosanoff, M.D.; Leva M. Handy, M.A., and Isabel R. Plesset, B.A. Price, $2. Pp. 37, with no illustrations. Princeton, N. J.: Psychological Review Company, 1937.

This study of twins throws a beam of light on a portion of human knowledge which is badly in need of illumination, the influence of heredity in nervous and mental disorders. The authors have laboriously collected a mass of information concerning twins from institutional and other sources. They secured records for the surprising total of 1,014 pairs of twins one or both of whom had a mental disorder and 308 pairs of normal twins, serving as controls. The present study deals with 366 pairs of twins, one or both of whom were mentally deficient. The monograph includes brief case histories for each of the 366 pairs. Twenty-six tables epitomize the data from the case histories. Chief dependence is placed on measurements of intelligence (method not stated), an intelligence quotient below 85 being indicative of mental deficiency. To be counted as "both affected," twins must have intelligence quotients which do not differ by more than five points. However, if a twin of a defective person is of normal intelligence but is affected with paralysis, epilepsy, psychosis, difficulty in child behavior, delinquency or adult criminality, the pair is counted as "both affected." Twins are divided into three groups: monozygotic, dizygotic of the same sex and dizygotic of the opposite sex.

The authors attempt to assign blame for mental deficiency on the following factors: pregerminal (hereditary), germinal, embryonic, fetal, intranatal and postnatal. If one twin was mentally deficient, the other was found to have an intelligence quotient within five points (or complicating paralysis, epilepsy, etc.) in the following proportions for the three groups: monozygotic twins, 91.3 per cent; dizygotic twins of the same sex, 61.4 per cent, and dizygotic twins of the opposite sex, 47.5 per cent. Humm found the corresponding proportion among singly born siblings of mentally defective persons to be 16.5 per cent. The authors explain the greater concordance of results for dizygotic twins of the same sex than for those of the opposite sex on the basis of sex linkage. Mistakes in classifying twins as dizygotic who were really monozygotic may be a readier explanation. Unexplained is the higher concordance for dizygotic twins than for siblings. When intelligence quotients which were within five points of each other were used as a test, the concordance for the three groups was as follows: monozygotic twins, 64.9 per cent; dizygotic twins of the same sex, 20.7 per cent, and dizygotic twins of the opposite sex, 14.6 per cent. The authors conclude that the difference in concordance between the monozygotic and the dizygotic twins is approximately 50 per cent, which represents the percentage of cases in which the deficiency is pregerminal, or the percentage of total etiologic factors of pregerminal origin (?). However, mental deficiency may not appear in spite of the presence of a hereditary factor, or it may appear in the absence of such a factor. Sex is a factor, since in twins of the opposite sex 27.6 per cent more males than females were affected.

In groups of twins (and their parents) and of singly born siblings who were mentally normal or superior, the authors found that females were more intelligent, and they computed that about one fifth of the superiority could be attributed to sex-linked genetic factors and four-fifths to the smaller liability of females to cerebral injuries at birth. The hereditary factor in mental deficiency is more important in patients with uncomplicated than in those with complicated mental deficiency and in patients with the least mental impairment. A germinal factor (injury to the ovum) is the sole cause of mongolism. Mental deficiency is more

common in twins than in the singly born, in monozygotic than in dizygotic twins, in males than in females, in the first born than the later born and in those who are born prematurely or are underweight at birth. These factors point to the importance of injuries at birth in the causation of mental deficiency. Injuries may not be demonstrable pathologically. The various manifestations of injury at birth presumably depend on the nature, extent and localization of the injury. However, even in infantile cerebral palsies the factor of heredity plays a part.

The authors have displayed great zeal in the collection of data and fairness in their presentation. The detailed study of normal twins by Newman, Freeman and Holzinger emphasizes the possibilities of a more comprehensive survey of the field of abnormality in twins. Such a survey, the authors believe, "should be undertaken under federal authority by some such body as the United States Public Health Service."

A Pediatrician in Search of Mental Hygiene. By Bronson Crothers, M.D. Cloth. Price, $2. Pp. 271. New York: Commonwealth Fund, Division of Publications, 1937.

"The whole idea of this volume," the author announces in the introduction, "is that it may be possible to approach psychiatry, psychology, education and social service without leaving pediatrics." The exploration of this possibility leads him to an informal, but sophisticated, review of such problems as the economics of medical practice, the history and present status of the mental hygiene movement, the results of increased use of laboratory methods on the relationship of the doctor and the patient and the effect of this in turn on the character of medical education. There is also a résumé of the rise to importance of the services of social workers in hospital practice. The status of the psychiatric social worker is of special concern to the author. Her ambiguous relation to medicine—especially what the author considers her "independence" of the doctor's supervision, in contrast to the position of his other technical assistants and deputies—and the implication in the title "psychiatric" that a person without medical training may have special knowledge in a medical field with which many physicians have little familiarity is candidly admitted as an obstacle to mutual understanding and cooperation.

Throughout there is manifest thorough familiarity with current attitudes toward the "confused but fascinating problems covered by the general term mental hygiene" on the part of the various interested groups, including psychiatrists, social workers and "propagandists." Dr. Crothers brings a frank recognition and appraisal of many important factors influencing attitudes of physicians to a discussion in which clarity is much needed. The physician emerges from these pages not as a person who is merely defensive about his ignorance of valid advances in psychiatry but as one who by long tradition, training and legal sanctions must first be prepared to give adequate care to sick people. Although willing to adopt any established innovations which will increase his efficiency in this primary duty, the physician is yet properly hesitant to undertake responsibilities and functions which may not be solidly based on scientific proof, for which he lacks training, and which, too, may be difficult to integrate with present conditions of medical practice under which he must earn his living.

In the third, and briefest, of the three sections into which the book is divided the author describes his own service in the wards of a children's hospital. This section is presented as the attempt on the part of one pediatrician to study and deal with the social, educational and economic problems of sick children as an integral part of the medical service rendered. An opportunity is afforded the interns and residents to study the "nonorganic" factors in the illnesses of children and their influence on treatment. The staff of this special unit, in addition to the regular medical personnel, includes a psychologist, a physical therapeutist and, apparently, a medical social worker. It is perhaps of interest that, after some trials, the services of a psychiatric social worker were not found indispensable.

The procedures used in management of situations uncovered by study are largely those which may be said to fall into the category of environmental or "external" manipulation. No mention is made of psychiatric treatment applied directly to the child, and the author specifically denies any attempt to duplicate the work of a psychiatrist. Any procedure which might involve influencing parental attitudes in any "psychiatric" sense are deliberately and carefully avoided. Observations made while the child is in the playroom or schoolroom of the hospital by all members of the staff are modestly referred to as part of the study and as "samples" of behavior.

Die Irradiation autonomer Reflexe: Untersuchungen zur Funktion des autonomen Nervensystems. VIII. By Alfred Schweitzer. Price, 40 Swiss francs. Pp. 376, with 38 illustrations. Basel, Switzerland: S. Karger, 1937.

This serious monograph, of over 300 pages and several thousand citations from the literature, gains and suffers from having been written from a particular point of view. The author concludes his work with the statement, translated roughly: "This work is no more than an expression of the conviction, for the field of reflex relations of the autonomic nervous system, that the individual behavior of an organ is intelligible only in relation to the whole." Reflex irradiation has the function of insuring changes in all organ systems appropriate to the altered activity of the primary effector. It is normal, orderly and useful. The book gains coherence in that many facts and interpretations are placed in relation to this theme; it suffers from a certain overpleading of the case, with repeated assertions and a tendency to quote "authorities."

The volume is about evenly divided into a general and a special portion. The former presents in order: evidence of irradiation in the central nervous system and the historical development of this knowledge; a good picture of the autonomic nervous system, again showing the rise of present concepts; the anatomic structures (nerve nets, etc.) permitting irradiation, considered mainly from the comparative point of view, and, finally, the problem of irradiation of autonomic reflexes in terms of methods of study and sources of error, laws of spread and conditions determining spread—state of the receptor, center, effector, strength of stimulus, etc.—which are illustrated chiefly by examples of depressor reflexes, such as the carotid body reflex.

The special section considers in more detail, and with explicit consideration of clinical applications, irradiation of reflexes from particular receptor systems: the skin and sensory nerves; eye, ear, and respiratory, digestive, urogenital and vascular systems. A large amount of interesting material is thus gathered, and the volume is in effect a treatise on the autonomic nervous system.

The Surgery of the Sympathetic Nervous System. By George E. Gask and J. Paterson Ross. Price, $4.50. Second edition. Pp. 191, with 49 illustrations. Baltimore: William Wood & Company, 1937.

Three years have elapsed since the first edition of this monograph was published. The whole book has been revised. Important changes have been made in the descriptions of the clinical grading and prognosis of Raynaud's disease; sections on the recognition of localized structural diseases of the arteries, on afferent pathways in the sympathetic nervous system and on the discussion of sympathectomy for relief from dysphagia are new.

This work is primarily an account of experiences in the surgical unit of St. Bartholomew's Hospital. It does not attempt to be a review of the whole field except when it coincides or disagrees with the observation of others. After a lucid description of the anatomic and physiologic characteristics of the sympathetic nervous system, sympathectomies for disorders of the circulation and the visceral motor mechanism and for relief from pain are discussed. Special attention is given to the selection of patients, which seems to be the key to success in operation. Less time is spent on technical considerations, as the authors believe

that general surgeons, well versed in the anatomic features of these regions, will encounter little difficulty.

The entire book is permeated by a sound and conservative, yet hopeful, attitude toward the future progress of surgical treatment of the sympathetic nervous system. In the concluding paragraph, the authors state: "The confession of our ignorance is to be regarded not as an excuse for despondency, but as a spur for renewed endeavor, for it must be realized that until more is known about the pathology of the sympathetic system, the place of surgery in the treatment of its disorders cannot be firmly established."

The monograph is highly recommended to physicians whose work brings them in contact with peripheral vascular disease and disturbed autonomic effector mechanisms.

Tumeurs intracraniennes. By Harvey Cushing. Translation by Jean Rossier. Price, 80 francs. Pp. 194. Paris: Masson & Cie, 1937.

This translation of Cushing's monograph on his series of 2,000 verified intracranial tumors is enhanced by the addition of translations of the follow-up reports which were published by Van Wagenen (Verified Brain Tumors, *J. A. M. A.* **102**:1454 [May 5] 1934) and Cairns (*Yale J. Biol. & Med.* **8**:421 [May] 1936). These appendixes are reviews of the end results, after an interval of ten years, of the patients who came under the care of Van Wagenen and Cairns during the term of residency of each under Dr. Cushing. This valuable material on such a large series of cases is well worth recording in any language, and the French may be felicitated on having the information accessible to them in their own tongue.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume II: Allgemeine Neurologie II. Experimentelle Physiologie. Compiled by K. Wachholder and others. Price, 110 marks. Pp. 561, with 137 illustrations. Berlin: Julius Springer, 1937.

This volume on experimental physiology contains excellent contributions to the general field of physiology of the nervous system. Wachholder has a good article on general physiologic behavior of muscle. There are a short, but good, article by Rademaker on the experimental physiologic reactions of the brain stem and two excellent articles by Dusser de Barenne on the physiologic aspects of the cerebellum and cortex. Wolff contributes a comprehensive article on conditioned reflexes. There are excellent chapters on the vegetative nervous system by Schieff and, especially, by Karplus. There is a short article by Kennard on the influence of the cortex on the autonomic nervous system. The volume is excellent and can be highly recommended.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume VII, part 2: Allgemeine Neurologie VIII, 2. Allgemeine Symptomatologie (der Nervenkrankheiten) einschliesslich Untersuchungsmethoden V, 2. Liquor, Hirnpunktion, Röntgenologie. By Edmund Forster and others. Price, 122 marks. Pp. 553, with 416 illustrations. Berlin: Julius Springer, 1936.

This volume is the second to be concerned with the spinal fluid. It contains a chapter by Guttmann on the physiologic and pathologic aspects of the mechanics and dynamics of the cerebrospinal fluid, which is well illustrated and concise, yet comprehensive. Steuvers contributes an article on roentgen diagnosis. Finally, there is an excellent monograph by Guttmann on the diagnosis of disorders of the brain and spinal cord by means of contrast mediums. This deals capably and in detail with encephalography, ventriculography and other methods of diagnosis of disorders of the central nervous system by means of contrast mediums. The bibliographies and illustrations are excellent. The volume can be highly recommended.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume XI: Spezielle Neurologie III. Erkrankungen des Rückenmarks und Gehirns I. Traumatische, präsenile und senile Erkrankungen. Zirkulationsstörungen. By Ernst Grünthal, Friedrich Hiller and Otto Marburg. Price, 104 marks. Pp. 550, with 148 illustrations. Berlin: Julius Springer, 1936.

This volume of the "Handbuch" deals with traumatic, presenile, senile and circulatory disturbances of the brain and spinal cord. Marburg contributes an excellent section on traumatic diseases of the brain and spinal cord. This in itself is a concise, yet complete, discussion of the role of trauma in disease of the central nervous system. There is a lengthy and excellent discussion of circulatory disturbances of the brain and spinal cord by Hiller. This volume of the monograph not only is extremely well written and planned but is well illustrated. Among other features it contains excellent diagrammatic illustrations of the arterial supply of the brain and brain stem. Grünthal contributes a useful chapter on presenile and senile diseases. The book is excellent in all respects and can be highly recommended. It contains extensive bibliographies.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume XIV: Spezielle Neurologie VI. Erkrankungen des Rückenmarks und Gehirns IV. Raumbeengende Prozesse. By Nils Antoni and others. Price, 91 marks. Pp. 450, with 270 illustrations. Berlin: Julius Springer, 1936.

This volume is concerned entirely with tumors and abscesses of the brain and spinal cord. Antoni contributes a good article on tumors of the spinal cord, which covers 122 pages and is well illustrated and comprehensive. The problem of intracranial tumors is discussed by A. J. McLean, who also contributes the chapter on tumors of the pituitary. Both these chapters are well written and cover all available material, but they suffer somewhat at times from too sketchy a treatment of the subject matter. Henneberg contributes a chapter on animal parasites of the central nervous system. The article on abscess of the brain by Wartenberg is rather brief, and that on abscess of the spinal cord by the same author is too sketchy for a system of this sort. The volume is not up to the standard of other volumes in this series, but will be found useful for the subjects discussed.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume XV. Spezielle Neurologie VII. Erkrankungen des Rückenmarks und Gehirns V. Endokrine Störungen. By Arthur Jores and Martin Nothmann. Price, 88 marks. Pp. 469, with 46 illustrations. Berlin: Julius Springer, 1937.

This volume is concerned entirely with endocrine diseases. It contains a good discussion of hyperthyroidism, myxedema, cretinism, parathyroid disease, disorders of the hypophysis, adrenal and thymus glands, and other diseases. It is a good volume and can be recommended to neurologists.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume XVI: Spezielle Neurologie VIII. Erkrankungen des Rückenmarks und Gehirns VI. Angeborene, früherworbene, heredofamiliäre Erkrankungen. By H. Josephy and others. Price, 233 marks. Pp. 1,172, with 442 illustrations. Berlin: Julius Springer, 1936.

This volume of the "Handbuch" contains many articles. It covers the wide field of the congenital heredofamilial diseases. One of the best articles in the volume is that by Wohlwill on cerebral infantile paralyses. This covers the cerebral diplegias, hemiplegias, paraplegias and allied conditions. It is a clear presentation of a complex subject, and is one of the best recent surveys of this problem of which the reviewer is aware. Gagel contributes a useful review of malformations of the spinal cord, a subject which has not been too frequently reviewed. This compilation of available knowledge on the problem is welcome. The myopathies are well treated from the pathologic standpoint by Slanck, and from the clinical side by Curschmann. The chapter on the pathologic lesions of the myopathies represents a welcome addition, since such studies are few. There are

a good section on the chronic progressive nuclear amyotrophies, by Marburg, and another, composed of several contributions, on extrapyramidal diseases. The pathologic manifestations of the latter have been inadequately handled.

The volume is comprehensive in content and structure. It is one of the best volumes available on the congenital and hereditary diseases of the nervous system and one of the best in this system of neurology. Extensive bibliographies are appended to almost all the articles. The volume can be unequivocally recommended to neurologists and all interested in the problem of congenital and hereditary diseases.

Krämpfe in Kindesalter. By Hans Bischoff. Price, 3.80 marks. Pp. 61. Stuttgart, Germany: Ferdinand Enke, 1937.

Professor Bischoff, director of the university pediatric clinic at Greifswald, Germany, has written this monograph from a rich experience with the convulsions of childhood. He says that spasmodic disturbances are closely connected with the idea of childhood not only by the laity but by the medical profession. Actually, no age is visited so frequently and, at the same time, so intensively by convulsive conditions. Therefore, there must be a disposition on the part of the child's organism to convulsions which is not to be found to such an extent at later ages. The anatomic structure of the central nervous system offers certain peculiarities. The brain of the newborn is not developed to completeness, for example, with regard to myelination. When susceptibility to convulsions is considered as a condition in which the convulsive threshold is low, the attack is to be regarded no longer as a physiologic but as a pathologic event. An endogenic factor is the preconditioning element on the basis of which an exogenic factor causes the fit.

Fifty pages are devoted to a schematic classification of children's convulsions; all the chronic possibilities are conscientiously described under the late lamented categories "organic" and "functional." Among the latter, *Vasomotorismus* is classified with hysteria as *rein funktionel.* No important data are presented.